

WO2007107706

Publication Title:

MULTIMERS QF HETEROCYCLIC COMPOUNDS AND THEIR USE

Abstract:

Abstract of WO2007107706

Covalent conjugates of two or more compounds, each having a structure as defined in any of WO2004/043924, WO2005/021509, WO2005/021512, WO2005/026123, WO2005/026124, WO2006/098683 and WO2006/098684, are inhibitors of human neutrophil elastase, useful in treatment of, for example, chronic obstructive pulmonary disease. Dimers of formula (IA) or (IB): wherein LINKER and the variable substituents are particular types of such multimers. Data supplied from the esp@cenet database - Worldwide

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(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
27 September 2007 (27.09.2007)

PCT

(10) International Publication Number
WO 2007/107706 A2

(51) International Patent Classification:
A61K 47/48 (2006.01)

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(21) International Application Number:
PCT/GB2007/000919

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(22) International Filing Date: 16 March 2007 (16.03.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0605469.6 17 March 2006 (17.03.2006) GB

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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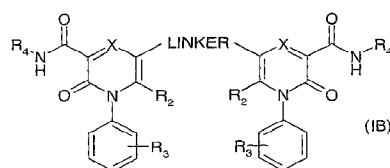
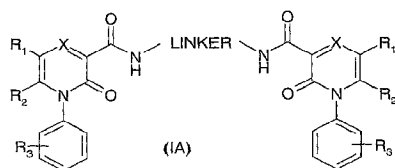
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Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MULTIMERS QF HETEROCYCLIC COMPOUNDS AND THEIR USE



(57) Abstract: Covalent conjugates of two or more compounds, each having a structure as defined in any of WO2004/043924, WO2005/021509, WO2005/021512, WO2005/026123, WO2005/026124, WO2006/098683 and WO2006/098684, are inhibitors of human neutrophil elastase, useful in treatment of, for example, chronic obstructive pulmonary disease. Dimers of formula (IA) or (IB); wherein LINKER and the variable substituents are particular types of such multimers.



WO 2007/107706 A2

MULTIMERS OF HETEROCYCLIC COMPOUNDS AND THEIR USE

Field of the Invention

This invention relates to multimeric heterocyclic compounds which are inhibitors of human neutrophil elastase (HNE), and their use in therapy, for example the treatment of chronic obstructive pulmonary disease (COPD) and other conditions where HNE is implicated.

Background to the invention

Human neutrophil elastase is a 32 kDa serine proteinase found in the azurophilic granules of neutrophils. It has a role in the degradation of a wide range of extracellular matrix proteins, including fibronectin, laminin, proteoglycans, Type III and Type IV collagens as well as elastin (Bieth, G. In *Regulation of Matrix accumulation*, Mecham, R. P. (Eds), Academic Press, NY, USA 1986, 217-306). HNE has long been considered to play an important role in homeostasis through repair and disposal of damaged tissues via degradation of the tissue structural proteins. It is also relevant in the defence against bacterial invasion by means of degradation of the bacterial body. In addition to its effects on matrix tissues, HNE has been implicated in the upregulation of IL-8 gene expression and also induces IL-8 release from the epithelial cells of the lung. In animal models of Chronic Obstructive Pulmonary Disease induced by tobacco smoke exposure both small molecule inhibitors and protein inhibitors of HNE inhibit the inflammatory response and the development of emphysema (Wright, J. L. et al. *Am. J. Respir. Crit. Care Med.* 2002, 166, 954-960; Churg, A. et al. *Am. J. Respir. Crit. Care Med.* 2003, 168, 199-207). Thus, HNE may play a role both in matrix destruction and in amplifying inflammatory responses in chronic respiratory diseases where neutrophil influx is a characteristic feature. Indeed, HNE is believed to play a role in several pulmonary diseases, including chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), acute respiratory distress syndrome (ARDS), pulmonary emphysema, pneumonia, severe asthma, sarcoidosis, bronchiectasis and lung fibrosis. It is also implicated in several cardiovascular diseases in which tissue remodelling is involved, for example, in heart failure and the generation of ischaemic tissue injury following acute myocardial infarction. Elevated HNE levels are also correlated with the severity of inflammation in inflammatory bowel disease (Silberer H et al, *Clin Lab.* 2005;51(3-4):117-26) and may play a role in impaired mucosal repair in patients with ulcerative colitis.

COPD is an umbrella term encompassing three different pathological conditions, all of which contribute to limitation of airflow: chronic bronchitis, emphysema and small-airway disease. Generally all three will exist to varying extents in patients presenting with COPD, and all three may be due to neutrophil-mediated inflammation, as supported by the increased number of neutrophils observed in bronchoalveolar leakage (BAL) fluids of COPD patients (Thompson, A. B.; Daughton, D.; et al. *Am. Rev. Respir. Dis.* 1989, 140, 1527-1537). The major pathogenic determinant in COPD has long been considered to be the protease-anti-protease balance (also known as the 'elastase:anti-elastase hypothesis'), in which an imbalance of HNE and endogenous antiproteases such as α_1 -antitrypsin (α_1 -AT), Secretory leukocyte protease inhibitor (SLPI) and pre-elafin leads to the various inflammatory disorders of COPD. Individuals that have a genetic deficiency of the protease inhibitor α_1 -antitrypsin (α_1 -AT) develop emphysema that increases in severity over time (Laurell, C. B.; Eriksson, S *Scand. J. Clin. Invest.* 1963 15, 132-140). An excess of HNE is therefore destructive, leading to the breakdown of pulmonary morphology with loss of elasticity and destruction of alveolar attachments of airways in the lung (emphysema) whilst simultaneously increasing microvascular permeability and mucus hypersecretion (chronic bronchitis).

Multimeric ligands consist of multiple binding domains which are tethered together through a suitable scaffold. Hence individual binding domains are linked together into a single molecule, increasing the probability that the multimer will bind simultaneously with multiple active sites resulting in high-affinity interactions (Handl, H. L. et al. *Expert Opin. Ther. Targets* 2004, 8, 565-586; Han, Y. F. et al., *Bioorg. Med. Chem.* 1999, 7, 2569-2575). Also, multiple binding interactions with relatively high off-rates can combine to yield an overall low off-rate for the multimeric ligand. Thus, a molecule consisting of a suitable linker and ligands may be expected to show advantage over the monomeric ligands alone in terms of potency and/or duration of action. Multimeric compounds are unlikely to be orally bioavailable (as predicted by Lipinski's "Rule of 5") which may be advantageous where an inhaled route of administration to the lungs is targeted, since even after inhaled administration, a large proportion of drug is likely to enter the GI tract. Thus such compounds may be expected to show reduced systemic exposure after inhalation administration and hence an improved toxicity profile over orally administered therapies.

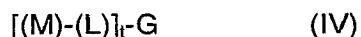
Compounds (herein described as "monomers") which are described as inhibitors of human neutrophil elastase are disclosed in WO2004/043924, WO2005/021509,

WO2005/021512, WO2005/026123, WO2005/026124, WO 2006/098683 and WO 2006/098684.

Summary of the Invention

5 A first aspect of the invention is a covalent conjugate of two or more compounds, each having a structure as defined in any of WO2004/043924, WO2005/021509, WO2005/021512, WO2005/026123, WO2005/026124, WO2006/098683 and WO2006/098684.

10 The covalent conjugate may be one having the formula:

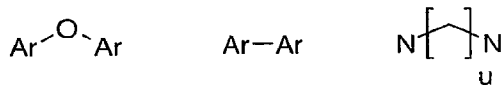


15 wherein

each M is independently a compound having a structure as defined in any of WO2004/043924, WO2005/021509, WO2005/021512, WO2005/026123, and WO2005/026124

20 t is 2 to 20;

G is optionally substituted aryl or heteroaryl; C₁-C₆ alkyl; cycloalkyl; nitrogen; a dendrimer or a group of any of formulae (V) to (VII):



(V)

(VI)

(VII)

25

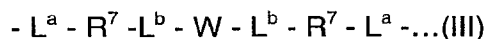
wherein

Ar is aryl or heteroaryl; and

u is 2-20;

each L is independently a linker group of Formula (III)

30



wherein

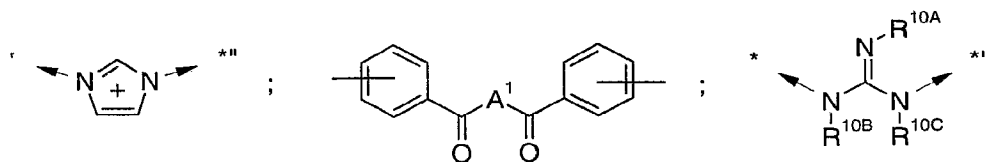
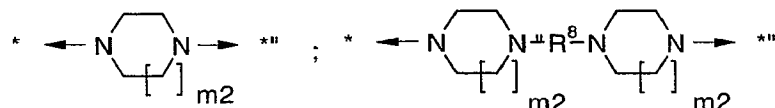
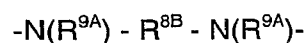
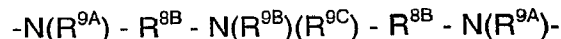
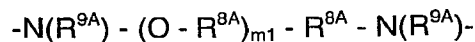
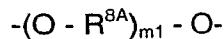
L^a is a bond or group -C(O)-;

L^b is a bond or group -C(O)-;

35

R⁷ is an alkylene or cycloalkylene group;

W is a bond or is selected from the following divalent radicals



wherein;

m1 is 1-4;

R^{8A} is an alkylene or cycloalkylene group;

R^{8B} is an alkylene or cycloalkylene group, or a group of Formula A²;

R^{9A} is hydrogen or alkyl;

one of R^{9B} or R^{9C} is a lone pair and the other is hydrogen or alkyl, or R^{9B} and R^{9C} are both alkyl, in which case the nitrogen to which they are attached is quaternary and carries a positive charge. Additionally, R^{9B} and R^{9C} may be joined together with the nitrogen to which they are attached to form a ring;

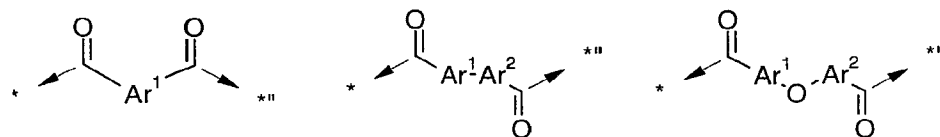
R^{10A} is hydrogen or alkyl;

R^{10B} and R^{10C} are independently hydrogen or alkyl, or alternatively R^{10B} and R^{10C} may be joined together to form a ring;

m2 is 1-3;

A^1 is selected from the groups $-N(R^{9A})-R^8-N(R^{9B})(R^{9C})-R^8-N(R^{9A})-$, and $-N(R^{9A})-R^8-N(R^{10B})C(=NR^{10A})(NR^{10C})-R^8-N(R^{9A})-$;

A^2 is selected from the groups of the formulae



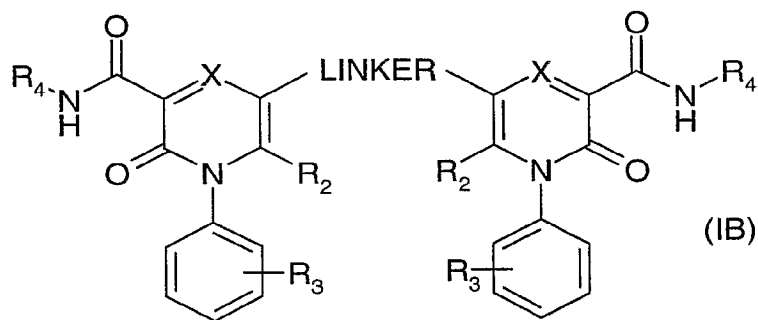
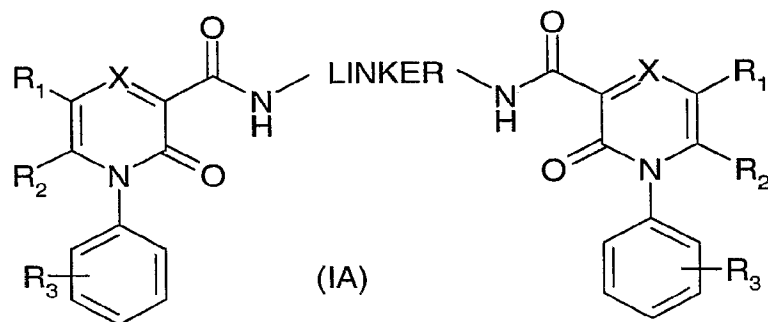
wherein Ar^1 , Ar^2 are independently an aryl or heteroaryl group;

or a pharmaceutically acceptable salt, solvate or N-oxide thereof.

Compounds of the invention may be described as dimers, when there are two moieties M. The linker L may however carry one or more further moieties M.

- 5 Presently, dimers are preferred. Furthermore, it is preferred that the moieties M be the same.

In a preferred aspect of the invention, there is provided a compound of formula (IA) or (IB), or a pharmaceutically acceptable salt thereof:



wherein

X represents -C= or -N=;

- 15 LINKER is a divalent linker radical;

R₁ is a group of formula Z-[Alk¹]_m-[X]_p-[Alk²]_n- wherein:

m, n and p are independently 0 or 1;

- 20 Z is hydrogen or an optionally substituted monocyclic carbocyclic or heterocyclic group having 3 to 7 ring atoms;

Alk¹ and Alk² are each independently an optionally substituted divalent C₁-C₆ alkenylene, C₂-C₆ alkenylene or C₂-C₆ alkynylene radical, which may optionally be interrupted by -O-, -S-, -S(=O)-, -S(=O)₂- or -NR₅- wherein R₅ is hydrogen, C₁-C₃ alkyl, or cyclopropyl; and

X is -O-, -S-, -S(=O)-, -S(=O)₂- or -NR₅- wherein R₅ is hydrogen, C₁-C₃ alkyl, or cyclopropyl;

R₂ represents hydrogen or C₁-C₆ alkyl;

or in the case of formula (IA), R₁ and R₂ taken together with the carbon atoms to which they are attached form a 5-, 6- or 7-membered carbocyclic or heterocyclic ring fused to the ring containing X and N, said fused ring being optionally substituted by one or more optional substituents, or one or more optionally substituted C₁-C₃ alkyl, C₂-C₃ alkenyl, or C₂-C₃ alkynyl groups;

or in the case of formula (IB), R₂ is linked with a carbon or nitrogen atom in the LINKER radical to form a 5-, 6- or 7-membered carbocyclic or heterocyclic ring fused to the ring containing X;

R₃ represents hydrogen, or 1 or 2 optional substituents, or 1 or 2 optionally substituted C₁-C₃ alkyl, C₂-C₃ alkenyl, or C₂-C₃ alkynyl;

R₄ represents a radical of formula -[Alk]_a-Q wherein

a is 0 or 1;

Alk represents an optionally substituted divalent C₁-C₄ alkenylene radical, which may terminate in or be interrupted by -O-, -S-, -S(=O)-, -S(=O)₂- or -NR₅- wherein R₅ is hydrogen, C₁-C₃ alkyl, or cyclopropyl;

Q is hydrogen, optionally substituted monocyclic carbocyclic or heterocyclic having from 3 to 6 ring atoms; or

R₄-NH- represents an optionally substituted monocyclic heterocyclic ring having 5 or 6 ring atoms and linked to the carbonyl via a ring nitrogen.

It will be appreciated that any compound of the invention may be used in the form of a prodrug.

Compounds of the invention may be useful in the treatment or prevention of diseases in which HNE is implicated, for example chronic obstructive pulmonary disease (COPD), chronic bronchitis, lung fibrosis, pneumonia, acute respiratory distress syndrome (ARDS), pulmonary emphysema, smoking-induced emphysema or cystic fibrosis, asthma, rhinitis, psoriasis, dermatitis, (atopic and non-atopic), Crohn's disease, ulcerative colitis, and irritable bowel disease.

Another aspect of the invention is a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable carrier or excipient. Preferred compositions are those adapted for pulmonary administration by inhalation.

Another aspect of the invention is the use of a compound of the invention for the manufacture of a medicament for the treatment or prevention of a disease or condition in which HNE is implicated. Thus, compounds of the invention may be used in a method of therapy, for the treatment of a patient suffering from a condition or disease as defined above.

Terminology

As used herein the term "(C₁-C₆)alkyl" means a straight or branched chain alkyl moiety having from 1 to 6 carbon atoms, including for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl and n-hexyl.

As used herein the term "(C₁-C₆)alkylene radical" means a divalent saturated hydrocarbon chain having from 1 to 6 carbon atoms .

As used herein the term "(C₂-C₆)alkenyl" means a straight or branched chain alkenyl moiety having from 2 to 6 carbon atoms having at least one double bond of either E or Z stereochemistry where applicable. The term includes, for example, vinyl, allyl, 1- and 2-butenyl and 2-methyl-2-propenyl.

As used herein the term "divalent (C₂-C₆)alkenylene radical" means a divalent hydrocarbon chain having from 2 to 6 carbon atoms, and at least one double bond.

As used herein the term "C₂-C₆ alkynyl" refers to straight chain or branched chain hydrocarbon groups having from two to six carbon atoms and having in addition one triple bond. This term would include for example, ethynyl, 1-propynyl, 1- and 2-butynyl, 2-methyl-2-propynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

As used herein the term "divalent (C₂-C₆)alkynylene radical" means a divalent hydrocarbon chain having from 2 to 6 carbon atoms, and at least one triple bond.

As used herein the unqualified term "carbocyclic" refers to a mono-, bi- or tricyclic radical having up to 16 ring atoms, all of which are carbon, and includes aryl and cycloalkyl.

As used herein the unqualified term "cycloalkyl" refers to a monocyclic saturated carbocyclic radical having from 3-8 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

As used herein the unqualified term "aryl" refers to a mono-, bi- or tri-cyclic carbocyclic aromatic radical, and includes radicals having two monocyclic carbocyclic aromatic rings which are directly linked by a covalent bond. Illustrative of such radicals are phenyl, biphenyl and naphthyl.

As used herein the unqualified term "heteroaryl" refers to a mono-, bi- or tri-cyclic aromatic radical containing one or more heteroatoms selected from S, N and O, and includes radicals having two such monocyclic rings, or one such monocyclic ring and one monocyclic aryl ring, which are directly linked by a covalent bond. Illustrative of such radicals are thienyl, benzthienyl, furyl, benzfuryl, pyrrolyl, imidazolyl, benzimidazolyl, thiazolyl, benzthiazolyl, isothiazolyl, benzisothiazolyl, pyrazolyl, oxazolyl, benzoxazolyl, isoxazolyl, benzisoxazolyl, isothiazolyl, triazolyl, benztriazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, indolyl and indazolyl.

As used herein the unqualified term "heterocyclyl" or "heterocyclic" includes "heteroaryl" as defined above, and in its non-aromatic meaning relates to a mono-, bi- or tri-cyclic non-aromatic radical containing one or more heteroatoms selected from S, N and O, and to groups consisting of a monocyclic non-aromatic radical containing one or more such heteroatoms which is covalently linked to another such

radical or to a monocyclic carbocyclic radical. Illustrative of such radicals are pyrrolyl, furanyl, thienyl, piperidinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, morpholinyl, piperazinyl, indolyl, morpholinyl, benzfuranyl, pyranyl, isoxazolyl, benzimidazolyl, methylenedioxyphenyl, ethylenedioxyphenyl, maleimido and succinimido groups.

Unless otherwise specified in the context in which it occurs, the term "substituted" as applied to any moiety herein means substituted with up to four compatible substituents, each of which independently may be, for example, (C₁-C₆)alkyl,

(C₁-C₆)alkoxy, hydroxy, mercapto (C₁-C₆)alkylthio, cyclopropyl, phenyl, monocyclic heterocyclyl having 5 or 6 ring atoms, halo (including fluoro, bromo and chloro), mono- di- or tri-fluoromethyl, mono-, di- or tri-fluoromethoxy, nitro, nitrile (-CN), oxo, -COOH, -COOR^A, -COR^A, -CONH₂, -CONHR^A, -CONR^AR^B, -SO₂OH, -SO₂OR^A, -SO₂R^A, -SO₂NH₂, -SO₂NHR^A, -SO₂NR^AR^B, -S(O)R^A, -NH₂, -NHR^A, -NR^AR^B, -OCONH₂, -OCONHR^A, -OCONR^AR^B, -OSO₂NH₂, -OSO₂NHR^A, -OSO₂NR^AR^B, -NHCOR^A, -NHCOOR^A, -NR^BCOOR^A, -NH₂SO₂OR^A, -NR^BSO₂OH, -NR^BSO₂OR^A, -NHCONH₂, -NR^ACONH₂, -NHCONHR^B, -NR^ACONHR^B, -NHCONR^AR^B, -NR^ACONR^AR^B, wherein R^A and R^B are independently a (C₁-C₆)alkyl, (C₃-C₆) cycloalkyl, phenyl or monocyclic heteroaryl having 5 or 6 ring atoms, or R^A and R^B when attached to the same nitrogen form a cyclic amino group such as morpholinyl, piperidinyl or piperazinyl. Where an optional substituent is or includes a phenyl or monocyclic heterocyclyl substituent having 5 or 6 ring atoms, that phenyl or heterocyclic ring may be substituted by any of the foregoing substituents except phenyl or monocyclic heterocyclyl having 5 or 6 ring atoms. An "optional substituent" or "substituent" may be one of the foregoing substituent groups.

As used herein the term "salt" includes base addition, acid addition and quaternary salts. Compounds of the invention which are acidic can form salts, including pharmaceutically acceptable salts, with bases such as alkali metal hydroxides, e.g. sodium and potassium hydroxides; alkaline earth metal hydroxides e.g. calcium, barium and magnesium hydroxides; with organic bases e.g. N-methyl-D-glucamine, choline tris(hydroxymethyl)amino-methane, L-arginine, L-lysine, N-ethyl piperidine, dibenzylamine and the like. Those compounds (I) which are basic can form salts, including pharmaceutically acceptable salts with inorganic acids, e.g. with hydrohalic acids such as hydrochloric or hydrobromic acids, sulphuric acid, nitric acid or phosphoric acid and the like, and with organic acids e.g. with acetic, tartaric, succinic, fumaric, maleic, malic, salicylic, citric, methanesulphonic, p-toluenesulphonic,

benzoic, benzenesulfonic, glutamic, lactic, and mandelic acids and the like. Those compounds (I) which have a basic nitrogen can also form quaternary ammonium salts with a pharmaceutically acceptable counter-ion such as chloride, bromide, acetate, formate, p-toluenesulfonate, succinate, hemi-succinate, naphthalene-bis sulfonate, methanesulfonate, xinafoate, and the like.

Depending on the methods, materials and solvents used in their manufacture, compounds of the invention may be isolated as hydrates or solvates. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

Compounds of the invention which contain one or more actual or potential chiral centres, because of the presence of asymmetric carbon atoms, can exist as a number of diastereoisomers with R or S stereochemistry at each chiral centre. The invention includes all such diastereoisomers and mixtures thereof.

In the preferred compounds of the invention of formula (IA) or (IB):

It is currently preferred that X is -C=.

R₂ is hydrogen or C₁-C₆ alkyl, for example methyl

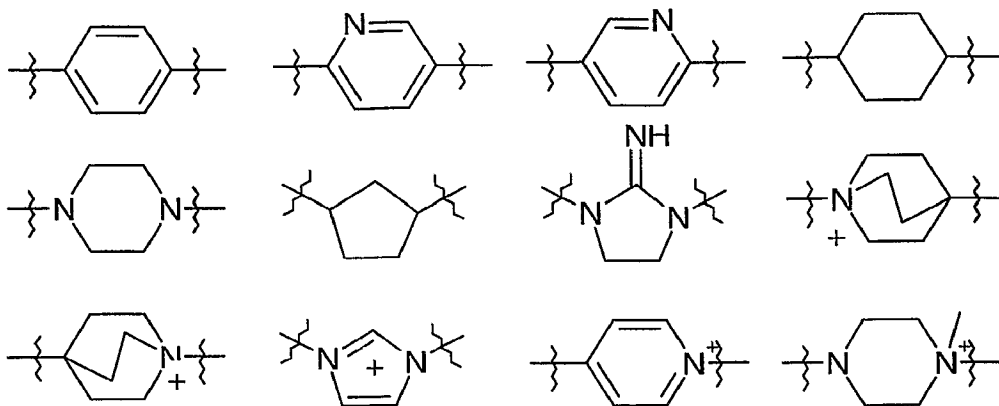
R₃ may represent, for example, 1 or 2 substituents, each independently selected from methyl, trifluoromethyl, fluoro, chloro, bromo, C₁-C₆ alkyl, -CN, C₁-C₆ alkoxy, -NO₂, -NR^AR^B wherein R^A and R^B are independently hydrogen or (C₁-C₆)alkyl, or R^A and R^B when attached to the same nitrogen form a cyclic amino group such as morpholinyl, piperidinyl or piperazinyl. In a currently preferred embodiment, R₃ represents a trifluoromethyl substituent in the meta position of the phenyl ring relative to the point of attachment of that phenyl ring to the rest of the molecule.

In the case of compounds of formula (IA), R₁ may be, for example, a group R₆-Y- wherein R₆ is optionally substituted phenyl or monocyclic heteroaryl ring having 5 or 6 ring atoms, and Y is a bond, -CH₂-, -C(=O)-, -O-, -S-, -S(=O)-, -S(=O)₂-, or -NH-. In such cases, it is currently preferred that Y is -S(=O)- and

R₆ is optionally substituted phenyl or pyridyl, in which optional substituents in the phenyl or pyridyl ring are selected from C₁-C₆ alkyl, C₁-C₆ alkoxy, C₂-C₆ alkenyl, C₂-C₆ alkynyl, methoxy, trifluoromethyl, trifluoromethoxy, cyano, fluoro, chloro, bromo, acetylamino, sulfonic acid, -NH₂, -NHR^A, -NR^AR^B, -NHCOR^A, -SO₂OH, -SO₂OR^A, -SO₂R^A, -SO₂NH₂, -SO₂NHR^A, -SO₂NR^AR^B, -OSO₂NH₂, -OSO₂NHR^A, -OSO₂NR^AR^B, -NHSO₂OR^A, -NR^BSO₂OH, -NR^BSO₂R^A, -NHSO₂R^A wherein R^A and R^B are independently hydrogen or (C₁-C₆)alkyl, or R^A and R^B when attached to the same nitrogen form a cyclic amino group, such as morpholinyl, piperidinyl or piperazinyl. However, R₆ may also be selected from, for example oxazolyl, thiazolyl, imidazolyl, triazolyl, pyrazolyl, pyrazinyl, pyrimidinyl, oxadiazolyl, furyl, and thienyl, any of which being optionally substituted, for example by C₁-C₆ alkyl, C₁-C₆ alkoxy, -CN, fluoro, chloro, bromo, or trifluoromethyl.

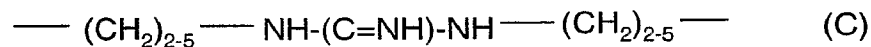
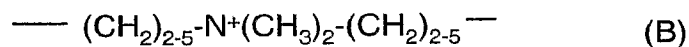
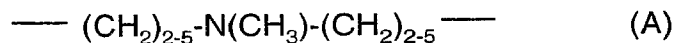
In the case of compounds of formula (IB), R₄ may, for example, be benzyl, optionally substituted in the phenyl ring thereof. In one currently preferred embodiment, R₄ is benzyl, optionally substituted in the 4-position of the phenyl ring thereof by a methylsulfonyl group.

In compounds (IA) and (IB) of the invention, the LINKER radical may be, for example, a divalent straight chain, saturated or unsaturated hydrocarbon radical having from 2 to 12 carbon atoms in the said chain, and wherein one or more carbons may be replaced by a divalent monocyclic or bicyclic carbocyclic or heterocyclic radical having from 3 to 7 ring atoms in the or each ring, or by -O-, -S-, -S(=O)-, -S(=O)₂-, -C(=O)-, -N(R^P)-, -N⁺(R^P)(R^Q)-, -C(=O)O-, -OC(=O)-, -C(=O)NR^A-, -NR^AC(=O)-, -S(O₂)NR^A-, -NR^AS(O₂)-, -NR^AC(=O)NR^B-, -NR^AC(=NR^A)NR^B-, -C(=NR^D)NR^E-, or -NR^EC(=NR^D)-, wherein R^A, R^B, R^D and R^E are independently hydrogen, C₁-C₆ alkyl, or C₃-C₆ cycloalkyl, and R^P and R^Q are independently hydrogen, C₁-C₆ alkyl, or C₃-C₆ cycloalkyl, HO-(C₁-C₆ alkyl)-, R^AR^BN-(C₁-C₆ alkyl)-, or HOC(=O)-(C₁-C₆ alkyl)-, or R^A and R^B, or R^D and R^E, or R^P and R^Q taken together with the nitrogens to which they are attached form a monocyclic heterocyclic ring of 5 to 7 ring atoms which may contain a further heteroatom selected from N, O and S. In the cases where one or more one or more -(CH₂)- groups of the LINKER radical is/are replaced by a divalent monocyclic or carbocyclic or heterocyclic radical, the said radical may be selected from, for example, the following:

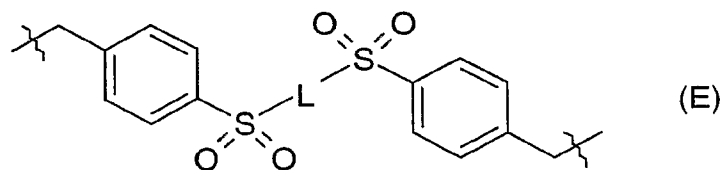
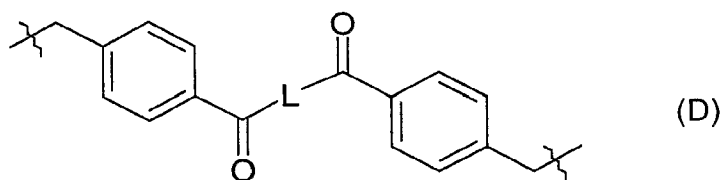


In the case of compounds of formula (IA) specific types of LINKER radicals have one of the following structures (A), (B) and (C):

5



In the case of compounds of formula (IA) other specific types of LINKER radicals have one of the following structures (D) and (E):

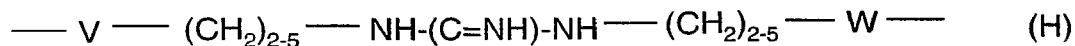
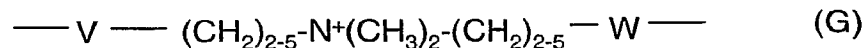
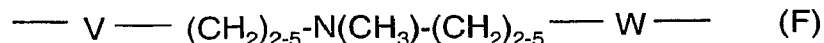


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wherein L is a radical of formula (A), (B) or (C) as in claim 12.

In the case of compounds of formula (IB) specific types of LINKER radicals have one of the following structures (F), (G) or (H):

15



wherein -V- is selected from -O-, -C(=O)NH- in either orientation, -C≡C- and
 5 -NR^A-, and -W is selected from -O-, -NHC(=O)- in either orientation, -C≡C-
 and -NR^A-, wherein R^A is (C₁-C₆)alkyl.

In many preferred compounds of the invention, the LINKER radical contains a
 quaternary nitrogen.

Specific examples of such dimeric compounds of formula (IA) and (IB) include those
 of the Examples herein, and especially Examples 19, 33, 17, 21, 28.

The therapeutic utility of the present compounds is pertinent to any disease that is
 15 known to be at least partially mediated by the action of human neutrophil elastase.
 For example, the present compounds may be beneficial in the treatment of chronic
 obstructive pulmonary disease (COPD), cystic fibrosis (CF), acute respiratory
 distress syndrome (ARDS), pulmonary emphysema, pneumonia and lung fibrosis.

The present invention is also concerned with pharmaceutical formulations
 comprising, as an active ingredient, a compound of the invention. Other compounds
 may be combined with compounds of this invention for the prevention and treatment
 of inflammatory diseases of the lung. Thus the present invention is also concerned
 20 with pharmaceutical compositions for preventing and treating inflammatory diseases
 25 of the lung comprising a therapeutically effective amount of a compound of the
 invention and one or more other therapeutic agents.

Suitable therapeutic agents for a combination therapy with compounds of the
 invention include: (1) a corticosteroid, for example fluticasone or budesonide; (2) a
 30 β₂-adrenoreceptor agonist, for example salmeterol or formeterol; (3) a leukotriene
 modulator, for example montelukast or pranlukast; (4) anticholinergic agents, for

example selective muscarinic-3 (M3) receptor antagonists such as tiotropium bromide; (5) phosphodiesterase-IV (PDE-IV) inhibitors, for example roflumilast or cilomilast; (6) an antitussive agent, such as codeine or dexamorphan; and (7) a non-steroidal anti-inflammatory agent (NSAID), for example ibuprofen or ketoprofen.

5

The weight ratio of the first and second active ingredients may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used.

- 10 The magnitude of prophylactic or therapeutic dose of a compound of the invention will, of course, vary with the nature of the severity of the condition to be treated and with the particular compound and its route of administration. It will also vary according to the age, weight and response of the individual patient. In general, the daily dose range will lie within the range of from about 0.001 mg to about 100 mg per
- 15 kg body weight of a mammal, preferably 0.01 mg to about 50 mg per kg, and most preferably 0.1 to 10 mg per kg, in single or divided doses. On the other hand, it may be necessary to use dosages outside these limits in some cases.

- Another aspect of the present invention provides pharmaceutical compositions which
- 20 comprise a compound of the invention and a pharmaceutically acceptable carrier. The term "composition", as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) (pharmaceutically acceptable excipients) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or
- 25 aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the invention, additional active ingredient(s), and pharmaceutically acceptable excipients.

30

- The pharmaceutical compositions of the present invention comprise a compound of the invention as an active ingredient or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts
- 35 prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic bases or acids and organic bases or acids.

Any suitable route of administration may be employed for providing a mammal, especially a human, with an effective dosage of a compound of the present invention. In therapeutic use, the active compound may be administered by any convenient, suitable or effective route. Suitable routes of administration are known to those skilled in the art, and include oral, intravenous, rectal, parenteral, topical, ocular, nasal, buccal and pulmonary. Delivery by inhalation is preferred.

Compositions suitable for administration by inhalation are known, and may include carriers and/or diluents that are known for use in such compositions. The composition may contain 0.01-99% by weight of active compound. Preferably, a unit dose comprises the active compound in an amount of 1 µg to 10 mg.

The most suitable dosage level may be determined by any suitable method known to one skilled in the art. It will be understood, however, that the specific amount for any particular patient will depend upon a variety of factors, including the activity of the specific compound that is used, the age, body weight, diet, general health and sex of the patient, time of administration, the route of administration, the rate of excretion, the use of any other drugs, and the severity of the disease undergoing treatment.

For delivery by inhalation, the active compound is preferably in the form of microparticles. They may be prepared by a variety of techniques, including spray-drying, freeze-drying and micronisation.

By way of example, a composition of the invention may be prepared as a suspension for delivery from a nebuliser or as an aerosol in a liquid propellant, for example for use in a pressurised metered dose inhaler (PMDI). Propellants suitable for use in a PMDI are known to the skilled person, and include CFC-12, HFA-134a, HFA-227, HCFC-22 (CCl₂F₂) and HFA-152 (CH₄F₂ and isobutane).

In a preferred embodiment of the invention, a composition of the invention is in dry powder form, for delivery using a dry powder inhaler (DPI). Many types of DPI are known.

Microparticles for delivery by administration may be formulated with excipients that aid delivery and release. For example, in a dry powder formulation, microparticles may be formulated with large carrier particles that aid flow from the DPI into the lung.

Suitable carrier particles are known, and include lactose particles; they may have a mass median aerodynamic diameter of greater than 90 μm .

In the case of an aerosol-based formulation, a preferred composition is:

5	Compound of the invention	24 mg / canister
	Lecithin, NF Liq. Conc.	1.2 mg / canister
	Trichlorofluoromethane, NF	4.025 g / canister
	Dichlorodifluoromethane, NF	12.15 g / canister

- 10 Compounds of the invention may be used in combination with other drugs that are used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which present compounds are useful. Such other drugs may be administered, by a route and in an amount commonly used therefore, contemporaneously or sequentially with a compound of the invention. When a
- 15 compound of the invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the invention is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the invention.

20

The agents of the invention may be administered in inhaled form. Aerosol generation can be carried out using, for example, pressure-driven jet atomizers or ultrasonic atomizers, preferably using propellant-driven metered aerosols or propellant-free administration of micronized active compounds

25 from, for example, inhalation capsules or other "dry powder" delivery systems.

25

The active compounds may be dosed as described depending on the inhaler system used. In addition to the active compounds, the administration forms may additionally contain excipients, such as, for example, propellants (e.g.

30 Frigen in the case of metered aerosols), surface-active substances, emulsifiers, stabilizers, preservatives, flavorings, fillers (e.g. lactose in the case of powder inhalers) or, if appropriate, further active compounds.

30

For the purposes of inhalation, a large number of systems are available with which

35 aerosols of optimum particle size can be generated and administered, using an inhalation technique which is appropriate for the patient. In addition to the use of adaptors (spacers, expanders) and pear-shaped containers (e.g. Nebulator®,

Volumatic®), and automatic devices emitting a puffer spray (Autohaler®), for metered aerosols, in particular in the case of powder inhalers, a number of technical solutions are available (e.g. Diskhaler®, Rotadisk®, Turbohaler® or the inhalers for example as described EP-A-0505321).

5

Methods of Synthesis

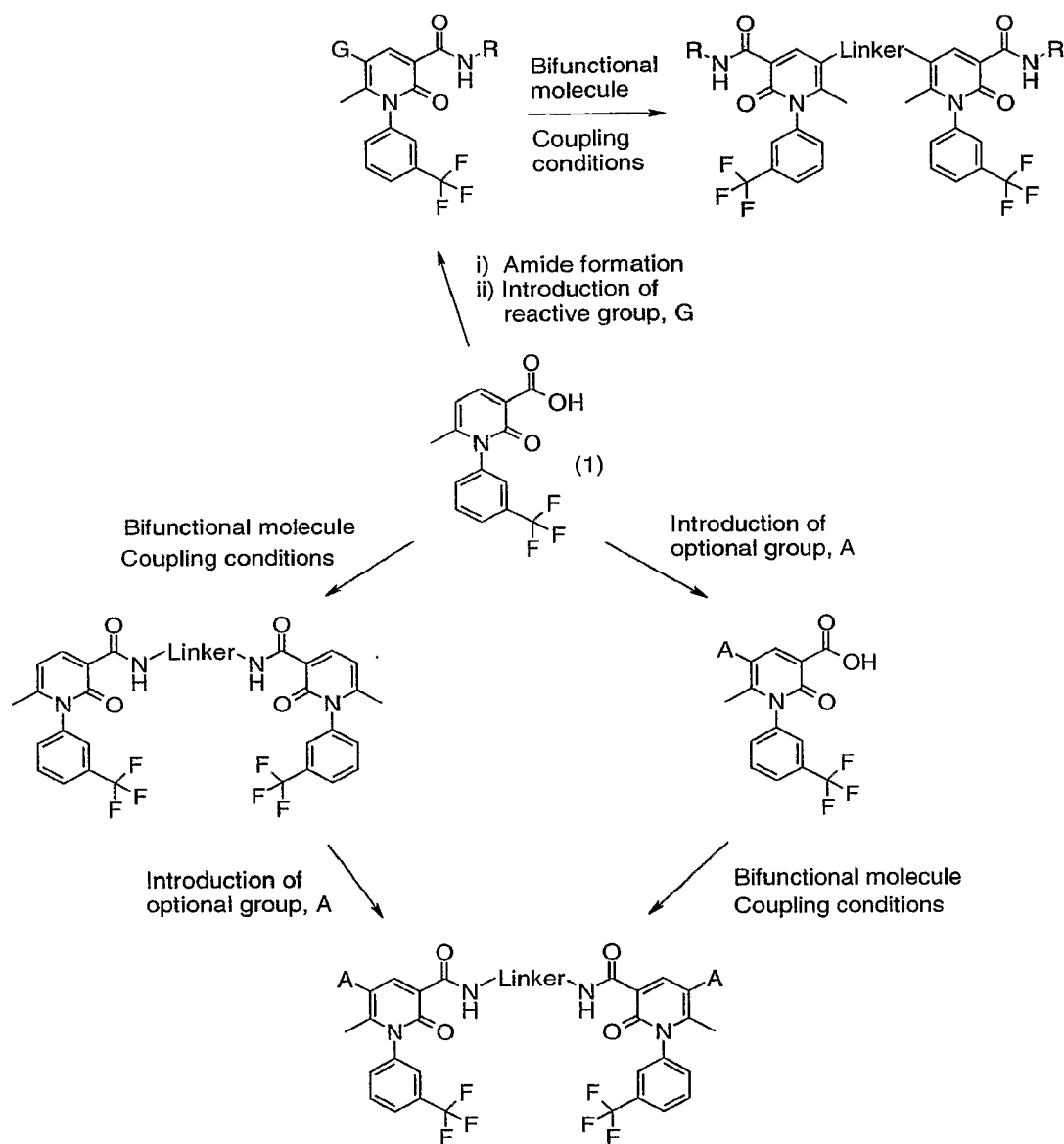
The compounds of the invention of the present invention can be prepared according to the procedures of the schemes and examples herein, using appropriate materials. Moreover, by utilising the procedures described with the disclosure contained herein, one of ordinary skill in the art can readily prepare additional compounds of the present invention claimed herein. The compounds illustrated in the examples are not, however, to be construed as forming the only genus that is considered as the invention. The examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds.

The compounds of the invention may be isolated in the form of their pharmaceutically acceptable salts, such as those described previously herein above. The free acid or base form corresponding to isolated salts can be generated by neutralisation with a suitable base or acid such as sodium hydroxide, potassium carbonate, acetic acid and hydrochloric acid and extraction of the liberated free acid or base into an organic solvent followed by evaporation. The free form isolated in this manner can be further converted into another pharmaceutically acceptable salt by dissolution in an organic solvent followed by addition of the appropriate acid or base and subsequent evaporation, precipitation, or crystallisation.

It may be necessary to protect reactive functional groups (e.g. hydroxy, amino, thio or carboxy) in intermediates used in the preparation of compounds of the invention to avoid their unwanted participation in a reaction leading to the formation of the compounds. Conventional protecting groups, for example those described by T. W. Greene and P. G. M. Wuts in "Protective groups in organic chemistry" John Wiley and Sons, 1999, may be used.

Compounds of the invention may be prepared according to the routes illustrated in Scheme 1. G is a group which can be reacted with a bifunctional molecule to effect dimerisation, such as an amino, iodo or carboxylic acid group. The bifunctional

molecule bears two other reactive groups, for example amino and carboxylic acid, which react, under suitable conditions, with group G to form a dimer. Where dimer formation is achieved through the carboxylic acid group in monomer (1), group A is an optional substituent which can be introduced before or after dimerisation, in one or more steps.



Scheme 1

The following non-limiting Examples illustrate the preparation and properties of specific compounds of the invention.

Preparative HPLC conditions:**HPLC system 1:**

C18-reverse-phase end-capped column (250 × 21.2 mm Gemini column with 5 µm particle size), eluting with a gradient of A: water + 0.1% formic acid; B: acetonitrile + 0.1 % formic acid at a flow rate of 17 ml/min and gradient of 1 %/min increasing in B. UV detection at 254 nm. After HPLC purification, pure fractions were combined and freeze-dried. Compounds were obtained as the formate salt where stated.

LC/MS Systems

The Liquid Chromatography Mass Spectroscopy (LC-MS) systems used:

LC-MS method 1

Waters Platform LC with a C18-reverse-phase column (30 × 4.6 mm Phenomenex Luna 3 µm particle size), elution with A: water + 0.1% formic acid; B: acetonitrile + 0.1 % formic acid. Gradient:

Gradient - Time	flow ml/min	%A	%B
0.00	2.0	95	5
0.50	2.0	95	5
4.50	2.0	5	95
5.50	2.0	5	95
6.00	2.0	95	5

Detection - MS, ELS, UV (100 µl split to MS with in-line UV detector)

MS ionisation method - Electrospray (positive and negative ion)

LC-MS method 2

Waters Micromass ZMD with a C18-reverse-phase column (30 × 4.6 mm Phenomenex Luna 3 µm particle size), elution with A: water + 0.1% formic acid; B: acetonitrile + 0.1 % formic acid. Gradient:

Gradient - Time	flow ml/min	%A	%B
0.00	2.0	95	5
0.50	2.0	95	5
4.50	2.0	5	95
5.50	2.0	5	95
6.00	2.0	95	5

Detection - MS, ELS, UV (100 µl split to MS with in-line UV detector)

MS ionisation method - Electrospray (positive and negative ion)

5 LC-MS method 3

Micromass Platform LCT with a C18-reverse-phase column (100 × 3.0 mm Higgins Clipseus with 5 µm particle size), elution with A: water + 0.1% formic acid; B: acetonitrile + 0.1 % formic acid. Gradient:

10	Gradient - Time	flow ml/min	%A	%B
	0.00	1.0	95	5
	1.00	1.0	95	5
	15.00	1.0	5	95
	20.00	1.0	5	95
15	22.00	1.0	95	5
	25.00	1.0	95	5

Detection - MS, ELS, UV (100 µl split to MS with in-line UV detector)

MS ionisation method - Electrospray (positive ion)

20

LC-MS method 4

Waters Micromass ZQ2000 with a C18-reverse-phase column (100 × 3.0 mm Higgins Clipseus with 5 µm particle size), elution with A: water + 0.1% formic acid; B: acetonitrile + 0.1 % formic acid. Gradient:

25

	Gradient - Time	flow ml/min	%A	%B
	0.00	1.0	95	5
	1.00	1.0	95	5
	15.00	1.0	5	95
30	20.00	1.0	5	95
	22.00	1.0	95	5
	25.00	1.0	95	5

Detection - MS, ELS, UV (100 µl split to MS with in-line UV detector)

35 MS ionisation method - Electrospray (positive ion)

NMR Spectrometers

NMR's were run on either a Varian Unity Inova 400 MHz spectrometer or a Bruker Avance DRX 400 MHz Spectrometer.

Abbreviations used in the experimental section:

AIBN = 2,2'-azobis(2-methylpropionitrile)

Al-N = neutral alumina

DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

DCE = 1,1-dichloroethane

10 DCM = dichloromethane

DME = 1,2-dimethoxyethane

DMF = *N,N*-dimethylformamide

DIPEA = di-isopropylethylamine

RT = room temperature

15 HATU = *O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluroniumhexafluorophosphate

IMS = industrial methylated spirit

NBS = *N*-bromosuccinimide

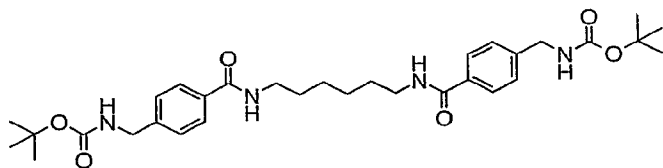
NIS = *N*-iodosuccinimide

20 TFA = trifluoroacetic acid

THF = tetrahydrofuran

Rt = retention time

SCX = strong cation exchange

Intermediate 1

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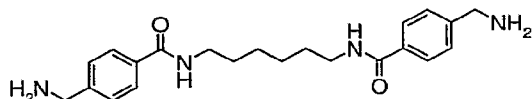
4-(*tert*-Butyloxycarbonylaminomethyl)benzoic acid (600 mg, 2.390 mmol), 1,6-diaminohexane (139 mg, 1.195 mmol), and DIPEA (1.5 ml) were dissolved in DMF (15 ml) and HATU (999 mg, 2.63 mmol) was added. The solution was allowed to stand at RT for 45 min. The DMF was evaporated and a 1:1 mixture of sat. aqueous

30 NaHCO₃ and EtOAc (50 ml) was added. After shaking, the mixture was filtered to give a white solid.

Yield 650 mg (93%)

$^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ = 8.36 (2H, t), 7.77 (4H, d), 7.43 (2 H, t), 7.28 (4H, d), 4.15 (4H, d), 3.22 (4H, q), 1.52 (4H, m), 1.39 (9H, s), 1.33 (4H, m).

Intermediate 2

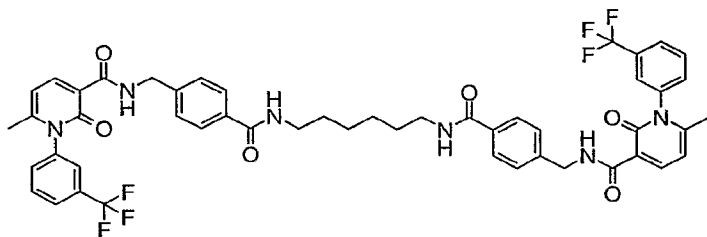


Intermediate 1 (430 mg, 0.738 mmol) was suspended in DCM (10 ml) and TFA (1 ml) was added. The reaction mixture was stirred at RT for 2 h before evaporation of the volatiles. The residue was loaded onto an IsoluteTM SCX-2 cartridge which was flushed with MeOH. The product was then eluted with 2M NH_3 in MeOH. The diamine was obtained as a white solid.

Yield: 176 mg (62%)

$^1\text{H-NMR}$ (400 MHz, MeOH-d_4): δ = 7.77 (4H, d), 7.41 (4H, d), 3.83 (4H, s), 3.37 (4H, t), 1.63 (4H, m), 1.46 (4H, m).

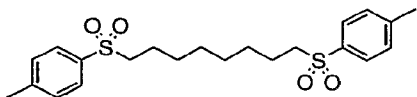
Intermediate 3



Intermediate 2 (176 mg, 0.461 mmol), 6-methyl-2-oxo-1-(3-trifluoromethylphenyl)-1,2-dihydropyridine-3-carboxylic acid (WO04043924) (274 mg, 0.921 mmol), and DIPEA (0.5 ml) were dissolved in DMF (10 ml) and HATU (385 mg, 1.013 mmol) was added. The solution was allowed to stand at RT for 1 h and the DMF was evaporated. The residue was dissolved in EtOAc (100 ml) and the solution was washed with sat. aqueous NaHCO_3 (80 ml), water (50 ml) and brine (40 ml). After drying (Na_2SO_4) the crude product was purified on an IsoluteTM Si II cartridge (10 g) eluting with 0-15% MeOH in EtOAc to give a pale yellow solid.

Yield: 438 mg (quant.)

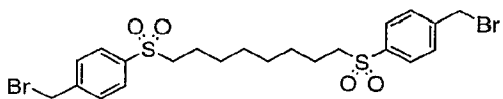
LC-MS (Method 1): Rt 3.72 min, m/z 941 [MH^+]

Intermediate 4

1,8-Dibromooctane (3.82 g, 14.04 mmol) was dissolved in DMF (50 ml) and sodium 4-toluenesulfinate hydrate (5.0 g, 28.09 mmol) was added. The suspension was stirred at RT for 24 h before evaporation of the DMF. The residue was partitioned between DCM (200 ml) and water (150 ml), the organic layer was separated and dried (Na₂SO₄), and the solvent was evaporated. Upon addition of Et₂O to the resulting oil, a white solid precipitated. The solid was filtered off and air-dried to give the desired product.

Yield: 2.65 mg (45%)

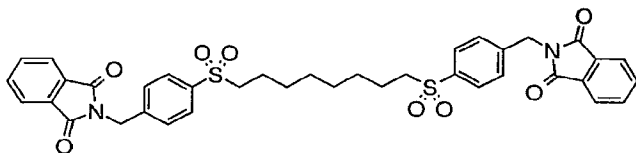
LC-MS (Method 2): Rt 3.93 min, m/z 423 [MH⁺]

Intermediate 5

A solution of Intermediate 4 (1.00 g, 2.37 mmol) in chloroform (20 ml) was treated with NBS (1.05 g, 5.93 mmol) and AIBN (39 mg, 0.24 mmol). The reaction mixture was refluxed for 4 h. After allowing to cool, the mixture washed with sat. aqueous NaHCO₃ (20 ml) and evaporated. Crystallisation from EtOAc furnished a white solid.

Yield: 472 mg (34%)

¹H-NMR (400 MHz, CDCl₃): δ = 7.87 (4H, d), 7.59 (4H, d), 4.52 (4H, s), 3.06 (4H, m), 1.71 (4H, m), 1.34 (4H, m), 1.24 (4H, m).

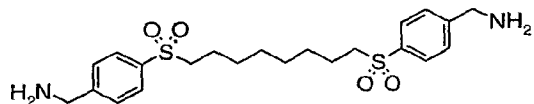
Intermediate 6

Intermediate 5 (586 mg, 1.01 mmol) was dissolved in DMF (15 ml) and potassium phthalimide (663 mg, 3.584 mmol) was added. The reaction was heated at 50°C for 2 h and then the DMF was evaporated. The residue was partitioned between chloroform (150 ml) and sat. aqueous NaHCO₃ (100 ml) and the organic layer was separated, dried (Na₂SO₄) and evaporated. The product was purified on an IsoluteTM Si II cartridge (10 g) eluting with DCM. The resulting solid was triturated with Et₂O/EtOAc/DCM giving a white solid.

Yield: 560 mg (78%)

LC-MS (Method 2): Rt 3.95 min, m/z 713 [MH⁺]

Intermediate 7

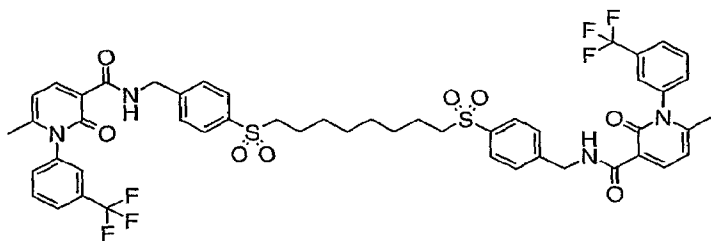


- 5 A solution of Intermediate 6 (534 mg, 0.763 mmol) and hydrazine hydrate (1 ml) in IMS (20 ml) and DCM (20 ml) was heated under reflux for 2.5 h. After cooling, the mixture was filtered and the filtrate was evaporated. The residue was loaded onto an Isolute™ SCX-2 cartridge (10 g) which had been conditioned with MeOH. After flushing the column with MeOH, the product was eluted with 2M NH₃ in MeOH.
- 10 Evaporation gave a white solid.

Yield: 319 mg (92%)

LC-MS (Method 2): Rt 1.69 min, m/z 453 [MH⁺]

Intermediate 8

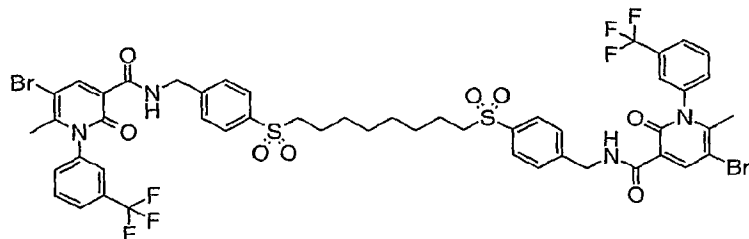


- 15 Intermediate 8 was prepared from 6-methyl-2-oxo-1-(3-trifluoromethylphenyl)-1,2-dihydropyridine-3-carboxylic acid (WO04043924) and Intermediate 7 using a similar procedure to that used in the synthesis of Intermediate 3.

Yield: 700 mg (44%)

LC-MS (Method 2): Rt 4.10 min, m/z 1011 [MH⁺]

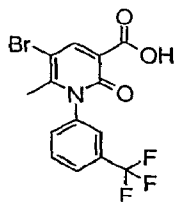
Intermediate 9



Intermediate 9 was prepared from Intermediate 8 using a similar procedure to that used in the preparation of Example 1.

Yield: (52%)

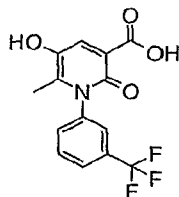
LC-MS (Method 2): Rt 4.57 min, m/z 1169 [MH⁺]

Intermediate 10

Bromine (0.25 ml, 4.5 mmol) was added to a stirred solution of 6-methyl-2-oxo-1-(3-trifluoromethylphenyl)-1,2-dihydropyridine-3-carboxylic acid (WO04043924) (1.0 g, 3.3 mmol) in acetic acid. After 2 h a further quantity of bromine (0.25 ml, 4.5 mmol) was added and stirring was continued for 2 h. After standing at RT for 18 h, the mixture was diluted with half sat. aqueous sodium thiosulphate (50 ml) and extracted with DCM (2 × 20 ml). The combined organics were washed with water (20 ml) and dried (Na₂SO₄) before evaporation of the solvent. The desired product was obtained as a pale yellow solid.

Yield: 1.24 g (100%)

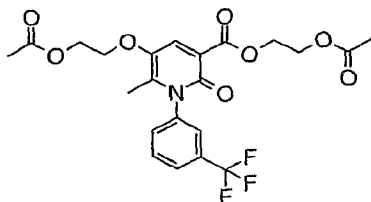
LC-MS (Method 1): Rt 3.49 min, m/z 376/378 [MH⁺]

Intermediate 11

Intermediate 10 (4.5 g, 11.97 mmol) was heated at 100°C in 5M aqueous NaOH (400 ml) for 2 h. The solution was allowed to cool and filtered. After diluting with water (200 ml), the solution was acidified by the addition of conc. aqueous HCl. The solution was extracted with EtOAc (3 × 200 ml) and the organic extracts were combined, washed with water (200 ml) and brine (100 ml), dried (Na₂SO₄) and evaporated. The residue was triturated with Et₂O and the brown solid was filtered and dried.

Yield: 475 mg (13%)

LC-MS (Method 1): Rt 3.01 min, m/z 314 [MH⁺]

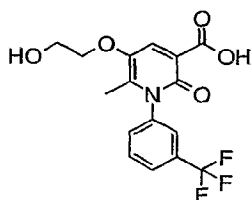
Intermediate 12

A solution of Intermediate 11 (470 mg, 1.50 mmol), 2-bromoethyl acetate (1.00 g, 5.99 mmol) and DBU (913 mg, 6.01 mmol) in DMF (3 ml) was heated under argon at 80°C for 1.5 h. On cooling the reaction mixture was diluted with EtOAc (50 ml) and 1M aqueous HCl (50 ml). The organic layer was separated, washed with water (40 ml) and brine (40 ml), dried (Na₂SO₄) and evaporated. The crude product was chromatographed on an Isolute™ Si II cartridge (20 g) eluting with 50-100% EtOAc in pentane.

Yield: 457 mg (63%)

LC-MS (Method 1): Rt 3.22 min, m/z 486 [MH⁺]

10 Intermediate 13

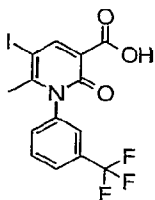


Intermediate 12 (457 mg, 0.924 mmol) was dissolved in MeOH (15 ml) and 2M aqueous NaOH (15 ml) was added. The solution was allowed to stand for 4 h and then filtered through celite. The Filtrate was acidified by the addition of conc. aqueous HCl and the product was extracted into EtOAc (100 ml). The organic extract was washed with water (70 ml) and brine (50 ml), dried (Na₂SO₄) and evaporated to give a brown oil which solidified on standing.

Yield: 309 mg (92%)

LC-MS (Method 1): Rt 2.83 min, m/z 358 [MH⁺]

Intermediate 14



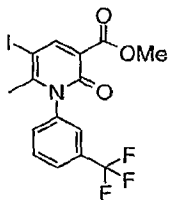
NIS (11.7 g, 0.05 mol) was added portion-wise to a stirred solution of 6-methyl-2-oxo-1-(3-(trifluoromethyl)phenyl)-1,2-dihydropyridine-3-carboxylic acid (WO04043924) (10.3 g, 0.035 mol) in a mixture of TFA (30 ml) and DCM (30 ml). Stirring was continued for 1.5 h the reaction mixture was partitioned between water (200 ml) and DCM (200 ml). The organic phase was separated and the aqueous was extracted further with DCM (2 × 100 ml). The organic extracts were combined, washed with

sat. aqueous sodium thiosulphate (100 ml), dried (Na_2SO_4) and concentrated to give a beige solid.

Yield: 13.6 g (93%)

LC-MS (Method 2): Rt 3.46 min, m/z 424 [MH^+]

5 Intermediate 15

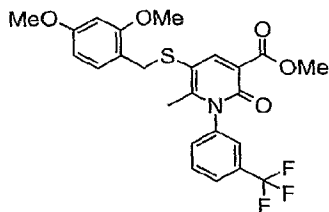


Intermediate 14 (4.00 g, 9.46 mmol) was suspended in a mixture of toluene (40 ml) and MeOH (40 ml) and (trimethylsilyl)diazomethane (10 ml, 2M in hexane) was added over 10 min. After nitrogen evolution had ceased a further portion of (trimethylsilyl)diazomethane (2 ml) was added. The solvents were evaporated and the residue was triturated with Et_2O to give a pale cream solid.

Yield: 3.21 g (78%)

LC-MS (Method 2): Rt 3.45 min, m/z 438 [MH^+]

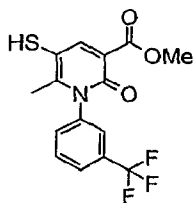
Intermediate 16



Intermediate 15 (3.76 g, 8.60 mmol) and 2,4-dimethoxybenzylthiol (*Synth. Commun.*, 1998, **28**, 3219) (1.90 g, 10.33 mmol) were dissolved in DME (75 ml) and the solution was degassed with argon. Copper (I) iodide (83 mg, 0.44 mmol) and potassium carbonate (2.37 g, 17.17 mmol) were added and the reaction mixture was heated at 90°C under an atmosphere of argon. After 17 h the mixture was allowed to cool and then filtered through celite. Evaporation gave a black-green residue which was chromatographed on an IsoluteTM Si II cartridge (50 g) eluting with 0-40% EtOAc in pentane. The impure fractions were combined and re-purified, and the pure fractions from both columns were evaporated to give a yellow foam.

Yield: 2.25 g (53%)

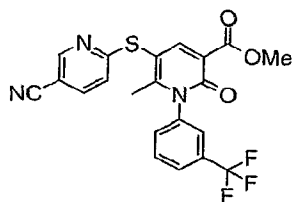
LC-MS (Method 2): Rt 4.05 min, m/z 494 [MH^+]

Intermediate 17

A solution of Intermediate 16 (2.25 g, 4.56 mmol) in DCE (90 ml) was treated with TFA (7 ml) and the solution was heated at reflux for 17 h under argon. The cooled reaction mixture was treated with a 1:1 mixture of pentane and Et₂O (100 ml) and a white solid was removed by filtration. The filtrate was evaporated and triturated with a mixture of pentane, DCM, Et₂O and EtOAc to afford a yellow solid.

Yield: 650 mg (42%)

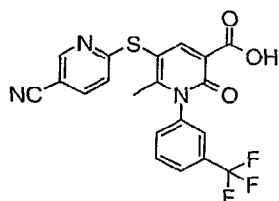
LC-MS (0Method 2): Rt 3.27 min, m/z 344 [MH⁺]

Intermediate 18

Intermediate 17 (320 mg, 0.933 mmol) and 6-chloronicotinitrile (129 mg, 0.93 mmol) were dissolved in 1,4-dioxane (15 ml) and caesium carbonate (304 mg, 0.93 mmol) was added. The reaction mixture was stirred at 40°C under argon. After 2 h the mixture was filtered and the filtrate evaporated. The residue was purified on an IsololuteTM Si II cartridge (10 g) eluting with 30 and 40% EtOAc in pentane. The product was obtained as a pale yellow solid.

Yield: 310 mg (75%)

LC-MS (Method 2): Rt 3.46 min, m/z 446 [MH⁺]

Intermediate 19

Intermediate 18 (400 mg, 0.674 mmol) was dissolved in 1,4-dioxane (10 ml) and 1M aqueous NaOH (6 ml) was added. After stirring for 1.5 h, the reaction mixture was

poured into 1M aqueous HCl (70 ml). The product was extracted with EtOAc (150 ml) which was washed with water (100 ml) and brine (50 ml), dried (Na_2SO_4) and evaporated to give a beige solid.

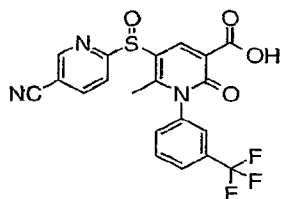
Yield: 290 mg (100%)

5 LC-MS (Method 2): Rt 3.55 min, m/z 432 [MH^+]

The material contained about 20% of the corresponding amide.

LC-MS (Method 2): Rt 3.03 min, m/z 450 [MH^+]

Intermediate 20

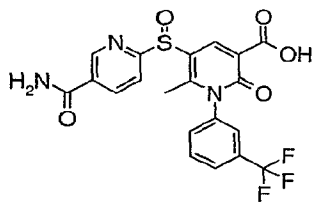


- 10 Intermediate 19 (290 mg, 0.67 mmol) was suspended in acetic acid (3.5 ml) and 30% aqueous hydrogen peroxide (0.9 ml) was added. The mixture was heated at 50°C for 2 h, after which time the solid had dissolved, and then diluted with water (20 ml) and filtered. After a few minutes a white solid had precipitated from the solution and was filtered off. The filtrate was purified using HPLC system 1 giving Intermediate 20 after
- 15 freeze-drying of the HPLC fractions. The white solid which had previously been obtained was combined with the material obtained from HPLC.

Yield: 76 mg (25%)

LC-MS (Method 1): Rt 3.30 min, m/z 448 [MH^+]

Intermediate 21



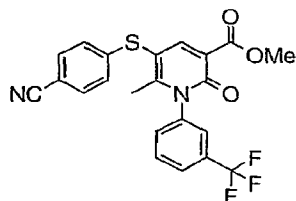
20

Intermediate 21 was obtained during the synthesis of Intermediate 20.

Yield: 24 mg (8%)

LC-MS (Method 1): Rt 2.74/2.80 min, m/z 466 [MH^+]

Intermediate 22



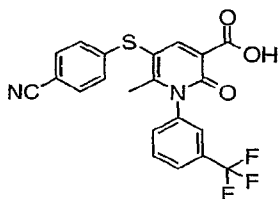
25

A solution of Intermediate 17 (846 mg, 2.47 mmol) and 4-iodobenzonitrile (565 mg, 2.47 mmol) in DME (20 ml) was degassed with argon. Copper (I) iodide (23 mg, 0.12 mmol) and potassium carbonate (681 mg, 4.93 mmol) were added and the reaction mixture was heated at 80°C under argon. After 2 h a further amount of 4-iodobenzonitrile (450 mg, 1.97 mmol) was added and heating was continued for a further 1 h. The mixture was allowed to cool and filtered. Evaporation gave a black-green oil which was purified on an Isolute™ Si II cartridge (25 g) eluting with 0-30% EtOAc in pentane. The desired product was obtained as a yellow gum which crystallised on standing.

Yield: 400 mg (36%)

LC-MS (Method 1): Rt 3.79 min, m/z 445 [MH⁺]

Intermediate 23

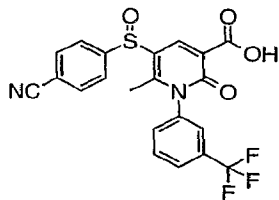


Intermediate 23 was prepared from Intermediate 22 using a procedure similar to that used in the synthesis of Intermediate 19.

Yield: (100%)

LC-MS (Method 1): Rt 3.78 min, m/z 431 [MH⁺]

Intermediate 24

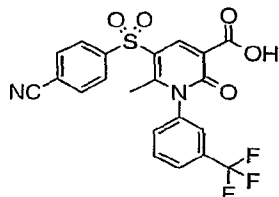


Intermediate 24 was prepared from Intermediate 23 by a similar method to that used to prepare Intermediate 20.

Yield: (25%)

LC-MS (Method 1): Rt 3.35 min, m/z 447 [MH⁺]

Intermediate 25

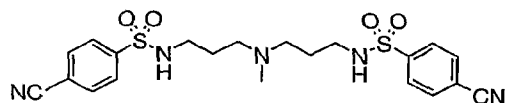


Intermediate 25 was obtained during the synthesis of Intermediate 24.

Yield: (7%)

LC-MS (Method 1): Rt 3.60 min, m/z 463 [MH⁺]

Intermediate 26

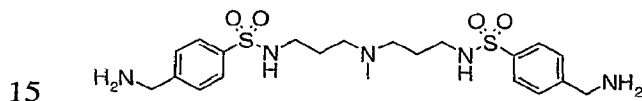


- 5 4-Cyanobenzene-1-sulfonyl chloride (4.0 g, 19.8 mmol) was added to a solution of 3,3'-diamino-*N*-methyldipropylamine (1.66 ml, 9.9 mmol) and triethylamine (3.0 ml, 21.6 mmol) in DMF (15 ml) at RT under nitrogen then stirred for 5 h. The mixture was poured into water (250 ml) and extracted with EtOAc (3 x 100 ml). The extracts were washed with water (2 x 100 ml) and brine (50 ml) before the organic phase was
- 10 isolated, dried (MgSO₄), filtered and concentrated. The crude product was triturated using cyclohexane, filtered and dried to afford Intermediate 26 as a white solid.

Yield: 2.69 g (57%)

LC-MS (Method 2): Rt 2.31 min, m/z 476 [MH⁺]

Intermediate 27

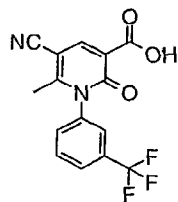


- Lithium aluminium hydride (1M in THF; 11 ml, 11 mmol) was added dropwise to a solution of Intermediate 26 (2.20 g, 4.62 mmol) in THF (30 ml) at -78°C under nitrogen then stirred for 1 h before the cooling bath was removed and the mixture allowed to warm to RT. The reaction was quenched using wet sodium sulphate and
- 20 left to stand overnight. It was filtered through celite using THF and concentrated *in vacuo*, then loaded onto an Isolute™ SCX-2 cartridge which was flushed with MeOH. The product was then eluted using 2M NH₃ in MeOH to give Intermediate 27 as a pale yellow glass.

Yield: 0.50 g (22%)

- 25 LC-MS (Method 2): Rt 0.24 min, m/z 484 [MH⁺]

Intermediate 28



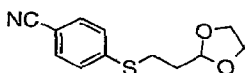
A mixture of Intermediate 14 (2.00 g, 4.73 mmol), zinc cyanide (1.8 g, 15 mmol) and Pd(PPh₃)₄ (80 mg, 0.069 mmol) in DMF (24 ml) was heated at 175°C for 2 min in the

microwave. The reaction mixture was poured into water (100 ml) and extracted with EtOAc (3 × 30 ml). The combined organic extracts were washed with water (2 × 50 ml) and brine (20 ml), dried (Na₂SO₄) and evaporated. Purification was achieved using a RediSepTM silica cartridge (25 g) eluting with pentane then Et₂O, followed by 1% acetic acid in Et₂O then 1% acetic acid in EtOAc. The impure fractions were combined and evaporated then triturated with IPA (30 ml) to give a further crop of a brown solid.

Yield: 410 mg (27%)

LC-MS (Method 2): Rt 3.23 min, m/z 323 [MH⁺]

10 Intermediate 29

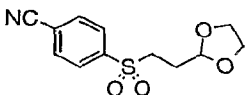


Sodium hydride (60% dispersion in mineral oil) (0.84 g, 21 mmol) was added to a solution of 4-cyanobenzenethiol (1.37 g, 10.11 mmol) in dry DMF (20 ml) under nitrogen. The reaction mixture was stirred at RT for 0.5 h before 2-(2-bromoethyl)-1,3-dioxolane (2.0 ml, 17.04 mmol) was added. After 2.5 h at RT, the reaction was quenched by careful addition of water (2 ml) under nitrogen with external cooling (ice/water bath). The mixture was partitioned between water (150 ml) and Et₂O (200 ml). The organic layer was separated, washed with water (100 ml), dried (Na₂SO₄) and evaporated to give pale yellow oil. The oil was purified on an IsoluteTM Si II cartridge (50 g) eluting with 40%, DCM in pentane, 70% DCM in pentane, 100% DCM and then 20% Et₂O in DCM. The required product was isolated as colourless oil.

Yield: 1.98 g (83%)

¹H-NMR (400 MHz, CDCl₃): δ = 7.53 (2H, d), 7.32 (2H, d), 5.00 (1H, t), 4.00 (2H, m), 3.90 (2H, m), 3.09 (2H, t), 2.06 (2H, m).

Intermediate 30



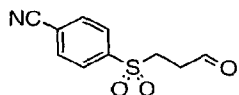
A solution of Intermediate 29 (1.94 g, 8.26 g) in MeOH (15 ml) was added drop wise, at RT, to a stirred slurry of Oxone (8.3 g, 13.5 mmol) in water (20 ml). Stirring was continued for 20 h and the mixture was partitioned between water (150 ml) and EtOAc (200 ml). The organic layer was separated, washed with water (100 ml) and brine (70 ml), dried (Na₂SO₄) and evaporated. The crude product was purified on an IsoluteTM Si II cartridge (50 g) eluting with DCM, 5% EtOAc in DCM, 10% EtOAc in

DCM, 15% EtOAc in DCM and then 20% EtOAc in DCM. The desired product was isolated as a white solid.

Yield: 2.08 g (95%)

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 8.05 (2H, d), 7.88 (2H, d), 4.96 (1H, t), 3.90 (2H, m), 3.84 (2H, m), 3.26 (2H, m), 2.10 (2H, m).

Intermediate 31

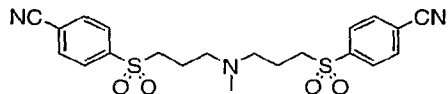


A solution of Intermediate 30 (2.05 g, 7.68 mmol) in acetone (60 ml) and hydrochloric acid (1M, 60 ml) was heated under nitrogen at 50°C for 20 h. The mixture was concentrated under reduced pressure and the residue partitioned between water (150 ml) and EtOAc (200 ml). The organic layer was separated, washed with water (100 ml), dried (Na_2SO_4) and evaporated. The residue was triturated with Et_2O to give the desired product as a white solid.

Yield: 1.45 g (85%)

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 9.76 (1H, s), 8.06 (2H, d), 7.90 (2H, d), 3.45 (2H, t), 3.03 (2H, t).

Intermediate 32



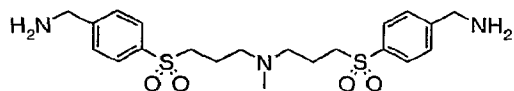
Methylamine solution in THF (2M, 3.0 ml, 5.98 mmol) was added to a solution of Intermediate 31 (3.0 g, 13.45 mmol) in DCM (100 ml) at RT under nitrogen. Sodium triacetoxyborohydride (8.97 g, 41.85 mmol) was added portion-wise to the above mixture over a period of 15 min. After stirring for a further 2 h, the reaction was quenched by careful addition of water (0.5 ml) and then partitioned between DCM (200 ml) and water (200 ml). The organic layer was separated, washed with water (100 ml), dried (Na_2SO_4) and evaporated to give a white solid. The crude product was split into two batches and each was purified with an IsoluteTM SCX-2 cartridge (50 g) which was flushed with DCM and 50% DCM in MeOH. The product was then eluted with 50% DCM in 2M NH_3 in MeOH. This product was further purified on an IsoluteTM Si II cartridge (50 g) with gradient elution from 20% EtOAc in DCM to 100% EtOAc. The desired product was isolated as a white solid.

Yield: 1.42 g (53%)

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ = 8.06 (4H, d), 7.89 (4H, d), 3.17 (4H, m), 2.40 (4H, t), 2.09 (3H, s), 1.85 (4H, m).

LC-MS (Method 1): Rt 0.32 and 2.08 min, m/z 446 [MH⁺]

Intermediate 33

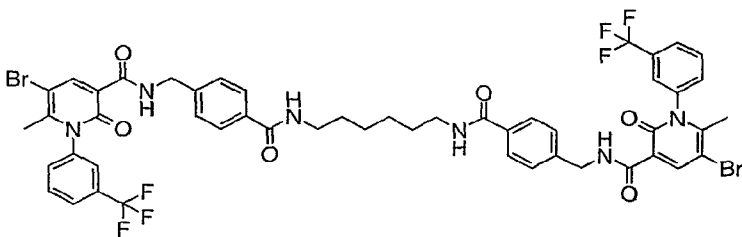


Intermediate 32 (300 mg, 0.67 mmol) and Raney Nickel 2800 (slurry in water, ca. 0.5 ml) in THF (15 ml) and IMS (30 ml) was vigorously stirred under an atmosphere of hydrogen at RT for 3 days. The catalyst was removed by filtration and the solvent evaporated. The residue was loaded onto an IsoluteTM SCX-2 cartridge (10 g) which was flushed with DCM and 50% DCM in MeOH. The product was then eluted with 50% DCM in 2M NH₃ in MeOH to give pale yellow oil (191 mg). This was used in the next reaction without further purification.

¹H-NMR (400 MHz, CDCl₃): δ = 7.79 (4H, d), 7.47 (4H, d), 3.93 (4H, s), 3.02 (4H, m), 2.26 (4H, t), 1.97 (3H, s), 1.75 (4H, m).

LC-MS (Method 1): Rt 0.32 min, m/z 454 [MH⁺]

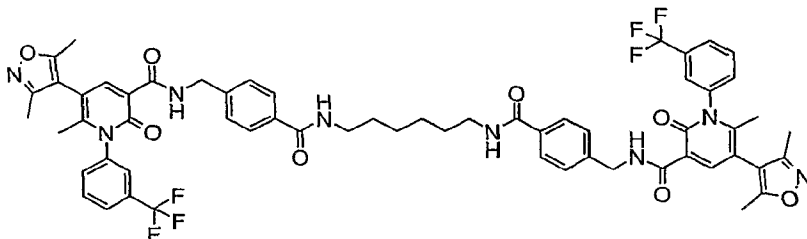
Example 1



Intermediate 3 (432 mg, 0.460 mmol) was dissolved in acetic acid (10 ml) and a solution of 0.42M bromine in acetic acid (2.4 ml, 1.01 mmol) was added. After stirring at RT for 30 min, a further portion of bromine solution (2.4 ml, 1.01 mmol) was added. After 30 min the solvent was evaporated and the product was purified on an IsoluteTM Si II cartridge (10 g) eluting with 80% EtOAc in pentane, 100% EtOAc, and then 10% MeOH in EtOAc. The impure fractions were combined and purified further by a similar chromatographic method. The desired product was obtained as a pale yellow solid.

Yield: 284 mg (56%)

LC-MS (Method 3): Rt 12.95 min, m/z 1098.82 [MH⁺]

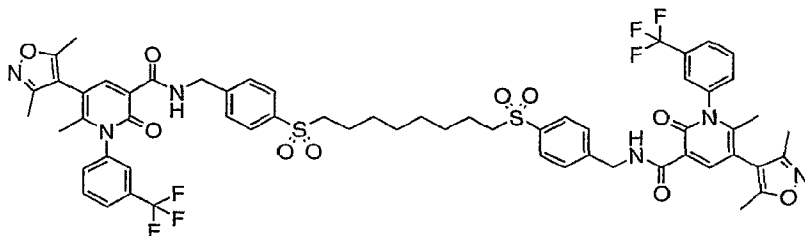
Example 2

A solution of Example 1 (238 mg, 0.217 mmol) in DME (9 ml) was split into two batches and to each was added 3,5-dimethylisoxazole-4-boronic acid (306 mg, 2.17 mmol), caesium carbonate (2.12 g, 6.51 mmol), water (0.5 ml) and Pd(PPh₃)₄ (13 mg, 0.011 mmol). The reaction vessels were de-gassed and then heated at 150°C for 15 min in the microwave. Further amounts of boronic acid (150 mg, 1.064 mmol) and catalyst (8 mg, 0.007 mmol) were added and heating was continued for 10 min. The two batches were combined and partitioned between EtOAc (150 ml) and water (100 ml). The organic layer was separated, washed with water (100 ml) and brine (50 ml), dried (Na₂SO₄) and evaporated. Purification was achieved using HPLC system 1 giving the product as a white solid.

Yield: 56 mg (22%)

¹H-NMR (400 MHz, DMSO-d₆): δ = 9.81 (2H, t), 8.30 (2H, t), 8.14 (2H, s), 7.95 (2H, m), 7.85 (2H, m), 7.87-7.71 (8H, m), 7.29 (4H, d), 4.49 (4H, m), 3.17 (4H, q), 2.27 (3H, s), 2.26 (3H, s), 2.08 (3H, s), 2.07 (3H, s), 1.75 (6H, s), 1.45 (4H, m), 1.27 (4H, m).

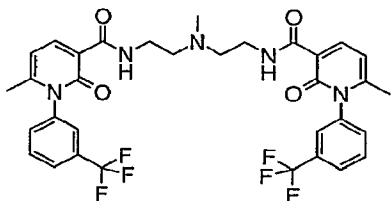
LC-MS (Method 3): Rt 12.16 min, m/z 1131.12 [MH⁺]

Example 3

Example 3 was prepared from Intermediate 9 using a procedure similar to that used in the synthesis of Example 2.

Yield: (46%)

LC-MS (Method 3): Rt 13.44 min, m/z 1200.97 [MH⁺]

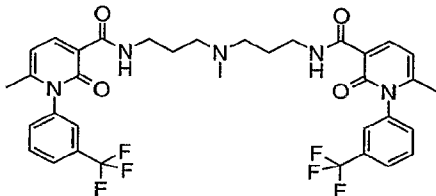
Example 4

2,2'-Diamino-*N*-methyldiethylamine (197 mg, 1.68 mmol), 6-methyl-2-oxo-1-(3-trifluoromethylphenyl)-1,2-dihydropyridine-3-carboxylic acid (WO04043924) (1.00 g, 3.367 mmol), and DIPEA (3 ml) were dissolved in DMF (50 ml) and HATU (1.14 mg, 3.70 mmol) was added. The solution was allowed to stand at RT for 3 h and the DMF was evaporated. The residue was dissolved in EtOAc (150 ml) and the solution was washed with sat. aqueous NaHCO₃ (100 ml), water (100 ml) and brine (50 ml). After drying (Na₂SO₄) the crude product was purified on an Isolute™ Si II cartridge (20 g) eluting with 0-20% MeOH in EtOAc to give a pale yellow solid. A small amount of material was purified further using HPLC system 1 yielding Example 4 as the free base.

Yield: 950 mg, (84%)

LC-MS (Method 3): Rt 8.16 min, m/z 676.19 [MH⁺]

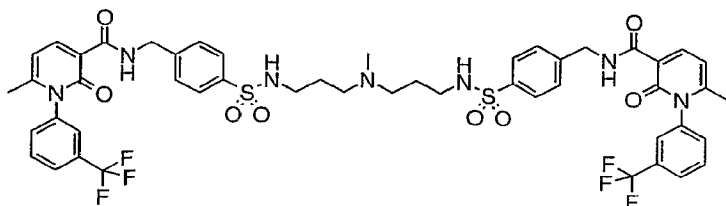
The following examples were prepared in a similar manner:

Example 5

Example 5 was prepared from 6-methyl-2-oxo-1-(3-trifluoromethylphenyl)-1,2-dihydropyridine-3-carboxylic acid (WO04043924) and 3,3'-diamino-*N*-methyl-dipropylamine. Purification was achieved using HPLC system 1 giving the formate salt.

Yield: (79%)

LC-MS (Method 3): Rt 8.21 min, m/z 704.34 [MH⁺]

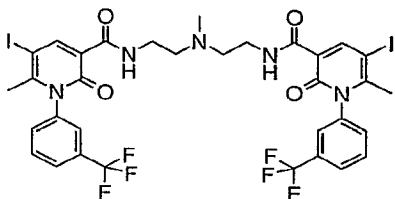
Example 6

Example 6 was prepared from 6-methyl-2-oxo-1-(3-trifluoromethylphenyl)-1,2-dihydropyridine-3-carboxylic acid (WO04043924) and Intermediate 27. The crude product was loaded onto an IsoluteTM SCX-2 cartridge (2 g) which was flushed with MeOH. The product was then eluted with 2M NH₃ in MeOH to give a white solid.

5 Yield: (13%)

LC-MS (Method 3): Rt 8.98 min, m/z 1042.41 [MH⁺]

Example 7



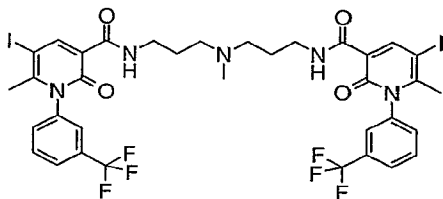
10 Example 7 was prepared from Intermediate 14 and 2,2'-diamino-*N*-methyldiethylamine. Purification was accomplished on a RediSepTM silica cartridge eluting with 0-10% MeOH in DCM.

Yield: (79%)

LC-MS (Method 3): Rt 9.26 min, m/z 928.06 [MH⁺]

15

Example 8



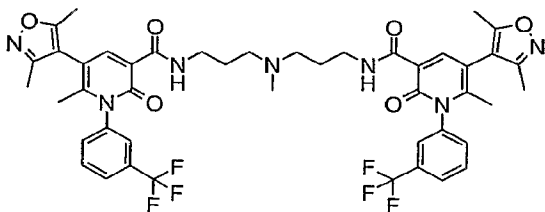
Example 8 was prepared from Intermediate 14 and 3,3'-diamino-*N*-methyldipropylamine. Purification on a RediSepTM silica cartridge eluting with 1-10% MeOH in DCM, gave a cream foam.

20

Yield: (21%)

LC-MS (Method 3): Rt 9.52 min, m/z 955.93 [MH⁺]

Example 9

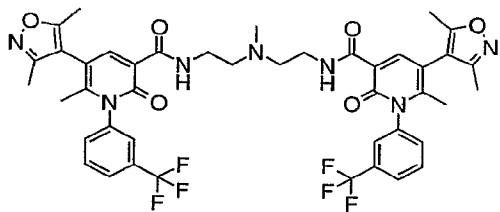


25

Example 9 was prepared from 5-(3,5-dimethylisoxazol-4-yl)-6-methyl-2-oxo-1-(3-trifluoromethylphenyl)-1,2-dihydropyridine-3-carboxylic acid (WO05026123) and 3,3'-diamino-*N*-methyldipropylamine. Purification was achieved using HPLC system 1 to afford the free base.

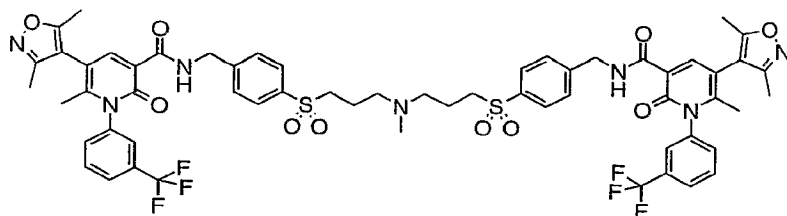
5

Yield: (4%)

LC-MS (Method 3): Rt 9.00 min, m/z 894.50 [MH⁺]**Example 10**

- 10 Example 10 was prepared from 5-(3,5-dimethylisoxazol-4-yl)-6-methyl-2-oxo-1-(3-trifluoromethylphenyl)-1,2-dihydropyridine-3-carboxylic acid (WO05026123) and 2,2'-diamino-*N*-methyldiethylamine. Purification was achieved using a RediSepTM silica cartridge eluting with DCM then DCM/EtOH/NH₄OH (400:8:1), followed by (200:8:1) and (100:8:1). Further purification on a RediSepTM C-18 silica cartridge eluting with 0-15 100% MeOH/H₂O gave a white solid.

Yield: (28%)

LC-MS (Method 3): Rt 8.98 min, m/z 866.39 [MH⁺]**Example 11**

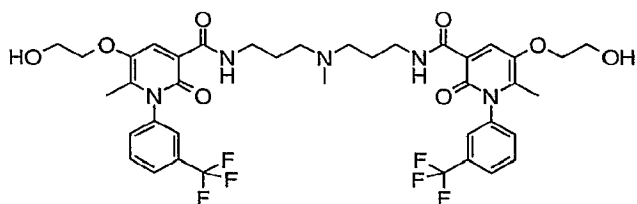
20

- Example 11 was prepared from 5-(3,5-dimethylisoxazol-4-yl)-6-methyl-2-oxo-1-(3-trifluoromethylphenyl)-1,2-dihydropyridine-3-carboxylic acid (WO05026123) and Intermediate 33. Purification was achieved using HPLC system 1 and ion exchange (IsoluteTM SCX-2) gave Example 11 as the free base.

25

Yield: 34%

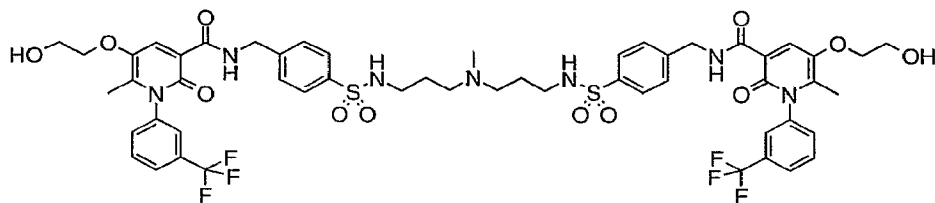
LC-MS (Method 4): Rt 9.25 min, m/z 1202.44 [MH⁺]

Example 12

Example 12 was prepared from Intermediate 13 and 3,3'-diamino-*N*-methylpropylamine. Purification was achieved using HPLC system 1 giving the free base.

Yield: (13%)

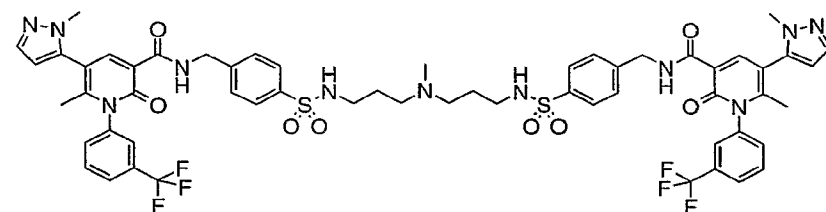
LC-MS (Method 3): Rt 7.57 min, m/z 824.41 [MH⁺]

Example 13

Example 13 was prepared from Intermediate 13 and Intermediate 27. Purification was achieved using HPLC system 1 giving the free base.

Yield: (17%)

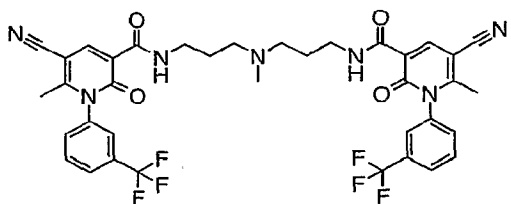
LC-MS (Method 3): Rt 8.41 min, m/z 1162.50 [MH⁺]

Example 14

Example 14 was prepared from 6-methyl-5-(2-methyl-2H-pyrazol-3-yl)-2-oxo-1-(3-trifluoromethyl-phenyl)-1,2-dihydropyridine-3-carboxylic acid (WO05026123) and Intermediate 27. Purification was achieved using HPLC system 1 giving the free base after ion exchange (IsoluteTM SCX-2).

Yield: (56%)

LC-MS (Method 4): Rt 8.66 min, m/z 1202.43 [MH⁺]

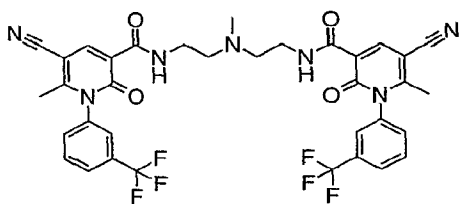
Example 15

- 5 Example 15 was prepared from Intermediate 28 and 3,3'-diamino-*N*-methyldipropylamine. Purification was achieved using HPLC system 1 giving the free base.

Yield: (23%)

LC-MS (Method 3): Rt 8.63 min, m/z 754.47 [MH⁺]

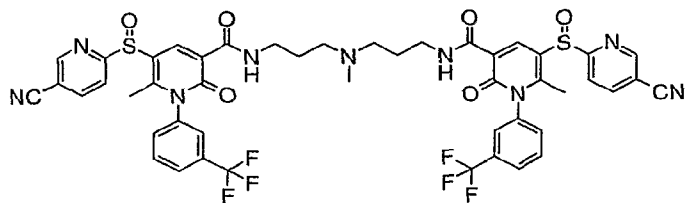
10 **Example 16**



Example 16 was prepared from Intermediate 28 and 2,2'-diamino-*N*-methyldiethylamine. Purification was achieved using HPLC system 1 giving the free base.

15 Yield: (10%)

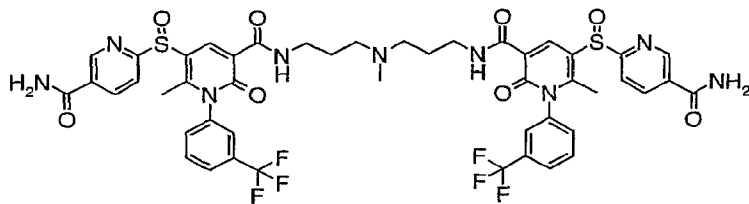
LC-MS (Method 3): Rt 8.60 min, m/z 726.42 [MH⁺]

Example 17

- 20 Example 17 was prepared from Intermediate 20 and 3,3'-diamino-*N*-methylpropylamine. Purification was achieved using HPLC system 1 giving the formate salt.

Yield: (22%)

LC-MS (Method 3): Rt 8.98 min, m/z 1004.35 [MH⁺]

Example 18

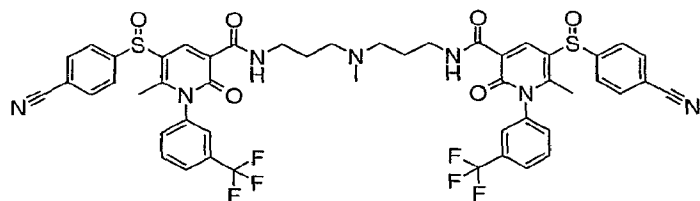
5

Example 18 was prepared from Intermediate 21 and 3,3'-diamino-*N*-methylpropylamine. Purification was achieved using HPLC system 1 giving the formate salt.

10

Yield: (15%)

LC-MS (Method 3): Rt 7.48 min, m/z 1040.26 [MH⁺]

Example 19

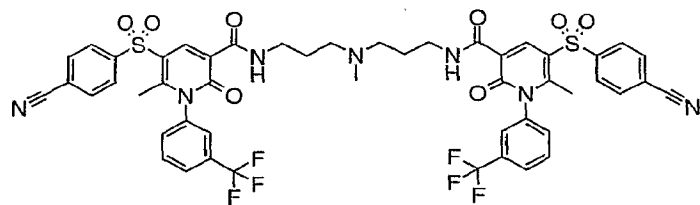
15

Example 19 was prepared from Intermediate 24 and 3,3'-diamino-*N*-methylpropylamine. Purification was achieved using HPLC system 1 giving the formate salt.

Yield: (27%)

20

LC-MS (Method 3): Rt 9.16 min, m/z 1002.37 [MH⁺]

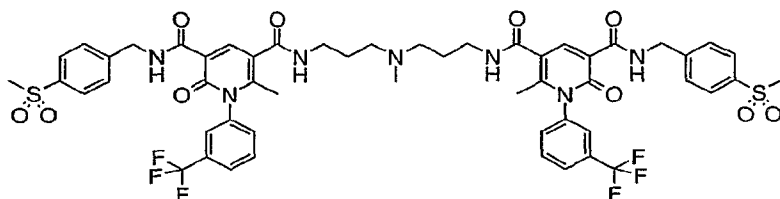
Example 20

Example 20 was prepared from Intermediate 25 and 3,3'-diamino-*N*-methylpropylamine. Purification was achieved using HPLC system 1 giving the formate salt.

Yield: (39%)

5 LC-MS (Method 3): Rt 9.80 min, m/z 1034.37 [MH⁺]

Example 21



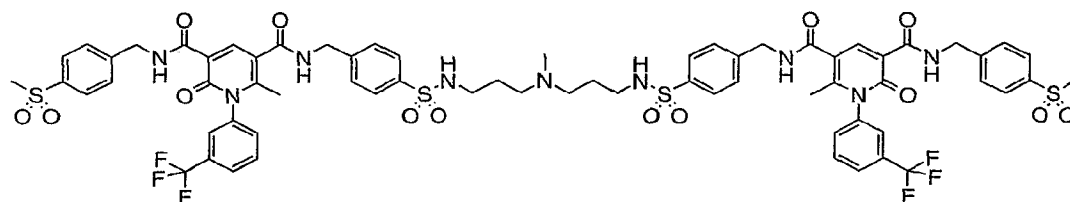
10

Example 21 was prepared from 5-(4-methanesulfonylbenzylcarbamoyl)-2-methyl-6-oxo-1-(3-trifluoromethylphenyl)-1,6-dihydropyridine-3-carboxylic acid (WO05026123) and 3,3'-diamino-*N*-methylpropylamine. Purification was achieved using HPLC system 1 and the free base was obtained by ion exchange (IsoluteTM SCX-2).

15 Yield: (42%)

LC-MS (Method 3): Rt 8.39 min, m/z 1126.48 [MH⁺]

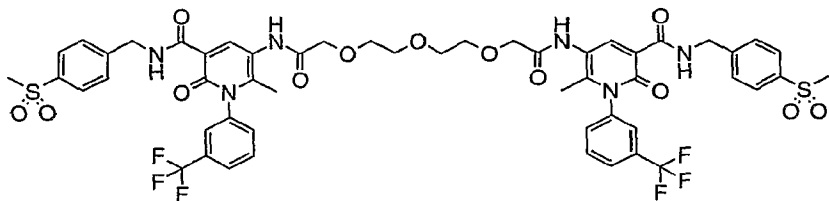
Example 22



20 Example 22 was prepared from 5-(4-methanesulfonylbenzylcarbamoyl)-2-methyl-6-oxo-1-(3-trifluoromethylphenyl)-1,6-dihydropyridine-3-carboxylic acid (WO05026123) and Intermediate 27. Purification was achieved using HPLC system 1 and the free base was obtained after ion exchange (IsoluteTM SCX-2).

Yield: (41%)

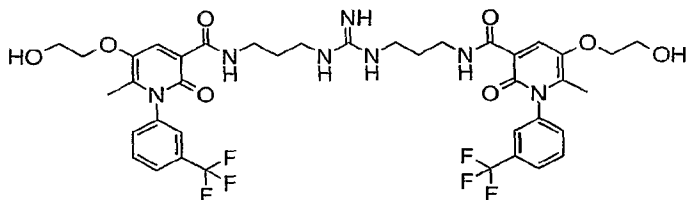
25 LC-MS (Method 4): Rt 8.61 min, m/z 1464.45 [MH⁺]

Example 23

Example 23 was prepared from 5-amino-6-methyl-2-oxo-1-(3-trifluoromethylphenyl)-
 1,2-dihydropyridine-3-carboxylic acid 4-methanesulfonylbenzylamide (WO
 2005026124) and 3,6,9-trioxaundecanoic acid. The crude product was purified using
 a RediSep™ silica cartridge, eluting with 0-10% MeOH in DCM, followed by
 trituration with Et₂O. Example 23 was obtained as a cream solid.

Yield: (25%)

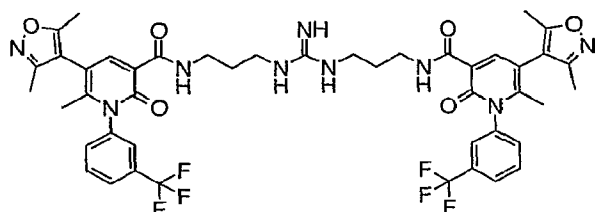
LC-MS (Method 3): Rt 10.25 min, m/z 1145.45 [MH⁺]

Example 24

{3-[N-(3-*tert*-Butoxycarbonylaminopropyl)-N'-(2,2,2-trifluoroacetyl)guanidino]propyl}-
 carbamic acid *tert*-butyl ester (*J. Org. Chem.*, 2003, **68**, 9416) (64 mg, 0.14 mmol)
 was dissolved in a 30% solution of TFA in DCM (18 ml). After 50 min the volatiles
 were evaporated and the residue was dissolved in DMF. Intermediate 13 (100 mg,
 0.28 mmol), DIPEA (181 mg, 1.40 mmol), and HATU (128 mg, 0.34 mmol) were
 added and the reaction was allowed to stand at RT for 2 h before evaporation of the
 solvent. The residue was dissolved in EtOAc (100 ml) and the solution was washed
 with sat. aqueous NaHCO₃ (100 ml), water (70 ml) and brine (50 ml), dried (Na₂SO₄)
 and evaporated. The resulting gum was dissolved in MeOH (8 ml) and a solution of
 potassium carbonate (200 mg, 1.45 mmol) in water (3 ml) was added. The mixture
 was stirred at RT for 1 h before evaporation of the MeOH. The residue was
 partitioned between EtOAc (100 ml) and water (100 ml). The organic layer was
 separated, washed with sat. aqueous NaHCO₃ (100 ml), water (70 ml) and brine (50
 ml), dried (Na₂SO₄) and evaporated. The residue was purified using HPLC system 1
 and the free base was obtained as a white solid.

Yield: 8 mg (7%)

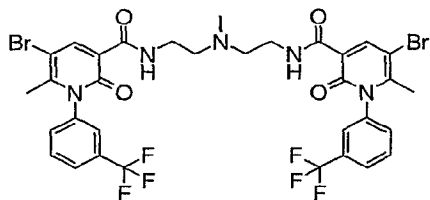
LC-MS (Method 3): Rt 7.68 min, m/z 852.33 [MH⁺]

Example 25

Example 25 was prepared from 5-(3,5-dimethylisoxazol-4-yl)-6-methyl-2-oxo-1-(3-trifluoromethylphenyl)-1,2-dihydropyridine-3-carboxylic acid (WO05026123) and {3-[*N*-(3-*tert*-butoxycarbonylaminopropyl)-*N'*-(2,2,2-trifluoroacetyl)guanidino]propyl}-carbamic acid *tert*-butyl ester (*J. Org. Chem.*, 2003, **68**, 9416) using a similar procedure to that used in the synthesis of Example 24. Purification was achieved using HPLC system 1 and the free base was obtained using an Isolute™ SCX-2 cartridge.

Yield: 8 mg (5%)

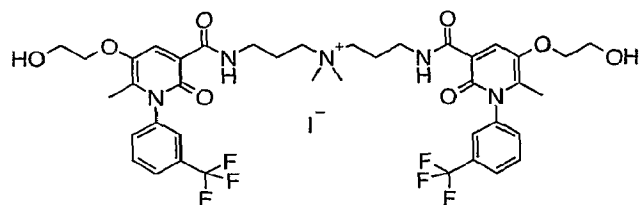
LC-MS (Method 3): Rt 9.15 min, m/z 922.51 [MH⁺]

Example 26

Example 4 (929 mg, 1.38 mmol) was dissolved in acetic acid (25 ml) and a 1.08M solution of bromine in acetic acid (3.8 ml, 4.13 mmol) was added. After 17 h, a further portion of bromine solution (1 ml) was added and stirring was continued for 4 h. The volatiles were evaporated and the residue was purified on a RediSep™ silica cartridge eluting with 0-8% MeOH in DCM. Trituration with Et₂O gave a white solid.

Yield: (39%)

LC-MS (Method 3): Rt 9.31 min, m/z 834.16 [MH⁺]

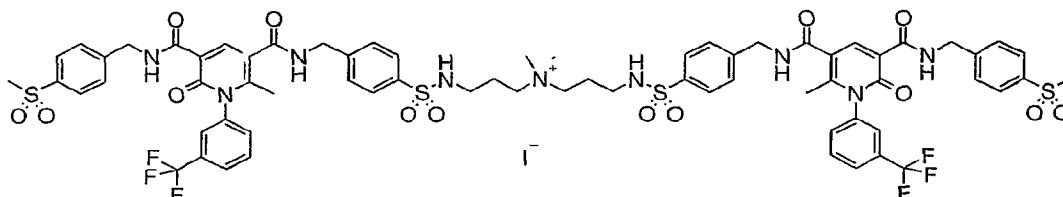
Example 27

Example 12 (13 mg, 0.016 mmol) was dissolved in acetonitrile (2 ml) and iodomethane (1 ml) was added. The solution was heated at 100°C for 20 min in the microwave. The volatiles were evaporated and the product was purified on an Isolute™ Al-N cartridge (2 g) eluting with DCM then 1% MeOH in DCM. After evaporation the pure product was dissolved in acetonitrile/water and freeze-dried to give a cream solid.

Yield: 7 mg (46%)

LC-MS (Method 3): Rt 7.50 min, m/z 838.48 [M⁺]

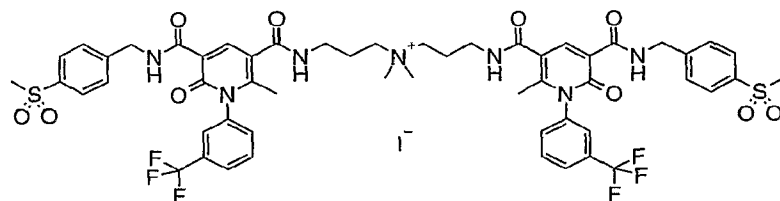
The following compounds were prepared in a similar manner:

Example 28

Example 28 was prepared from Example 22

Yield: (60%)

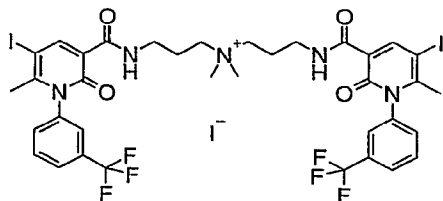
LC-MS (Method 4): Rt 8.63 min, m/z 1477.85 [M⁺]

Example 29

Example 29 was prepared from Example 21.

Yield: (76%)

LC-MS (Method 4): Rt 7.94 min, m/z 1140.00 [M⁺]

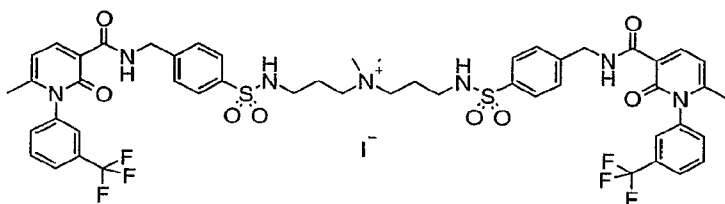
Example 30

Example 30 was prepared from Example 8.

Yield: (23%)

5

LC-MS (Method 3): Rt 9.30 min, m/z 970.14 [M⁺]

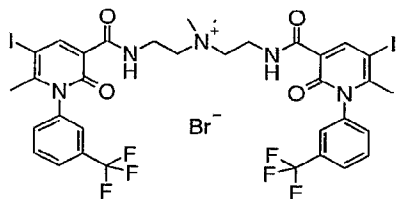
Example 31

Example 31 was prepared from Example 6.

10

Yield: (63%)

LC-MS (Method 3): Rt 9.04 min, m/z 1056.46 [M⁺]

Example 32

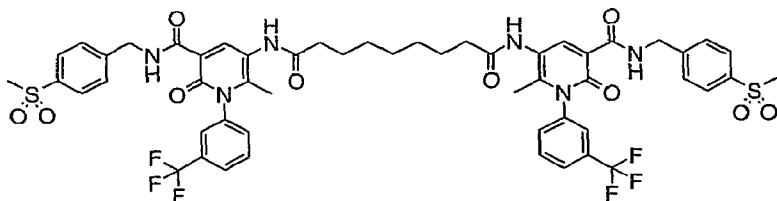
15

Example 7 (200 mg, 0.215 mmol) was dissolved in acetonitrile (15 ml) and a 30% solution of bromomethane in acetonitrile (7 ml) was added. The solution was heated for 42 h at 80°C in a steel reaction vessel. A further portion of bromomethane solution (7 ml) was added and heating was continued for 18 h. The volatiles were evaporated and the product was purified on an IsoluteTM Al-N cartridge (10 g) eluting with 0-5% MeOH in DCM. Trituration with EtOAc gave a pale yellow solid.

20

Yield: (55%)

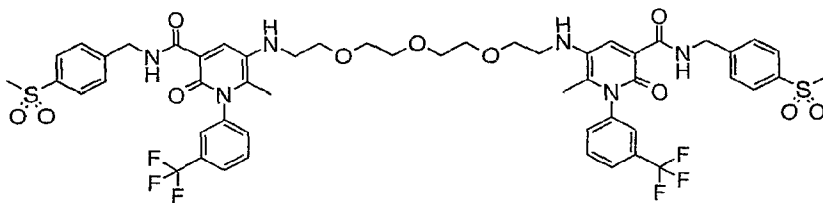
LC-MS (Method 3): Rt 9.36 min, m/z 942.02 [M⁺]

Example 33

5-Amino-6-methyl-2-oxo-1-(3-trifluoromethylphenyl)-1,2-dihydropyridine-3-carboxylic acid 4-methanesulfonylbenzylamide (WO05026124) (50 mg, 0.1 mmol) was dissolved in DCM (2 ml). DIPEA (26 mg, 0.2 mmol) and azeloyl chloride (10.5 mg, 0.045 mmol) were added and the solution was allowed to stand at RT for 1 h. After diluting with EtOAc (20 ml), the solution was washed with 1M aqueous HCl (20 ml) and 1M aqueous NaOH (20 ml), dried (MgSO₄) and evaporated. Chromatography on a RediSep™ silica cartridge, eluting with 0-7% MeOH in DCM, gave a solid which was triturated with Et₂O. Example 33 was obtained as a cream solid.

Yield: (70%)

LC-MS (Method 4): Rt 10.82 min, m/z 1111.38 [MH⁺]

Example 34

To a solution of 5-amino-6-methyl-2-oxo-1-(3-trifluoromethylphenyl)-1,2-dihydropyridine-3-carboxylic acid 4-methanesulfonylbenzylamide (WO05026124) (100 mg, 0.2 mmol) and {2-[2-(2-oxoethoxy)ethoxy]ethoxy}acetaldehyde (23 mg, 0.1 mmol) in DCE (3 ml) was added acetic acid (15 mg, 0.25 mmol) and sodium triacetoxymethylborohydride (64 mg, 0.3 mmol). The mixture was stirred at RT for 17 h. A further portion of reducing agent (64 mg, 0.3 mmol) was added followed, after 1.5 h, by a further portion of reducing agent (64 mg, 0.3 mmol) and {2-[2-(2-oxoethoxy)ethoxy]ethoxy}acetaldehyde (23 mg, 0.1 mmol). After 17 h, the reaction was diluted with EtOAc (50 ml). The solution was washed with 1M aqueous NaOH (40 ml) and the aqueous was extracted with a further portion of EtOAc (50 ml). The combined organic extracts were dried (MgSO₄) and evaporated. Chromatography on a RediSep™ silica cartridge, eluting with 0-8% MeOH in DCM, gave a solid. Further purification was achieved on another RediSep™ cartridge eluting with 0-20% MeOH

in EtOAc and the resulting solid was triturated with Et₂O. Example 34 was obtained as a fawn solid.

Yield: 7 mg (6%)

LC-MS (Method 3): Rt 10.90 min, m/z 1117.46 [MH⁺]

5

Biological Results

The compounds of the examples were tested for their inhibitory activity towards HNE.

Fluorescent peptide substrate

- 10 Assays were performed in 96-well plates at a total assay volume of 100 µl. The final concentration of the enzyme (human leukocyte elastase, Sigma E8140) was 0.00036 units/well. A peptide substrate (MeO-Suc-Ala-Ala-Pro-ValAMC, Calbiochem #324745) was used, at the final concentration of 100 µM. The final concentration of DMSO was 1% in the assay buffer (0.05M Tris.HCl, pH 7.5, 0.1M NaCl; 0.1M CaCl₂;
15 0.0005% brij-35).

- The enzymatic reaction was started by adding the enzyme. The enzymatic reaction was performed at RT and after 30mins stopped by adding 50µl soybean trypsin inhibitor (Sigma T-9003) at a final concentration of 50µg/well. Fluorescence was read
20 on the FLEXstation (Molecular Devices) using 380 nm excitation and 460 nm emission filters. The potency of the compounds was determined from a concentration series of 10 concentrations in range from 1000 nM to 0.051 nM. The results are means of two independent experiments, each performed in duplicate.

25 *Using Fluorescently labelled elastin*

- Assays were performed in 96-well plate at a total assay volume of 100 µl. The final concentration of the enzyme (human leukocyte elastase, Sigma E8140) was 0.002 units/well. Fluorescently labelled, solubilised elastin from bovine neck ligament (Molecular Probes, E-12056) was used at the final concentration of 15 µg/ml. The
30 final concentration of DMSO was 2.5% in the assay buffer (0.1M Tris-HCL, pH8.0, containing 0.2 mM sodium azide).

- The enzymatic reaction was started by adding the enzyme. The enzymatic reaction was performed at RT and read after 120 minutes. Fluorescence was read on the
35 FLEXstation (Molecular Devices) using 485 nm excitation and 530 nm emission filters. The potency of the compounds was determined from a concentration series of 10 concentrations in range from 25000 nM to 1nM.

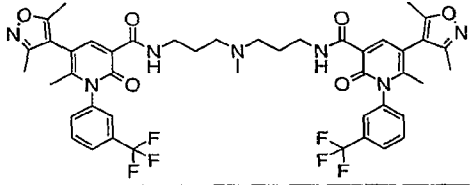
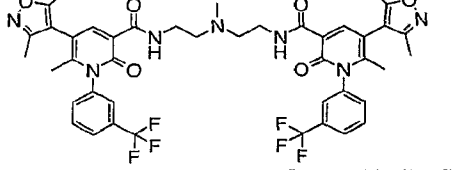
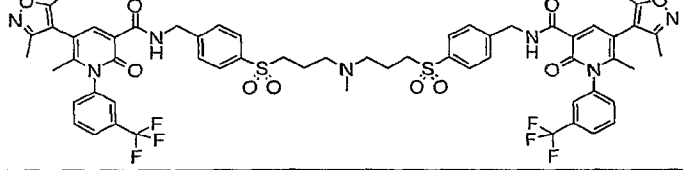
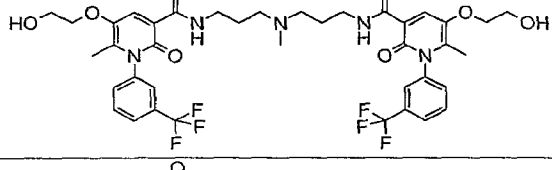
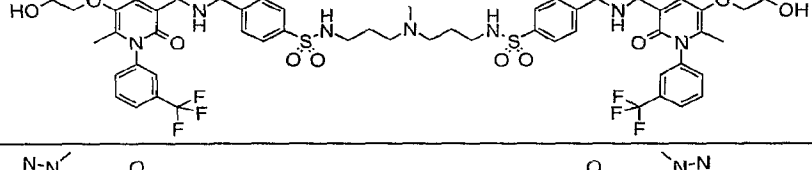
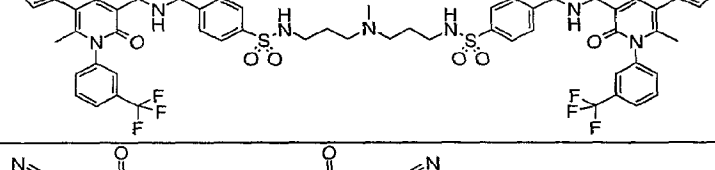
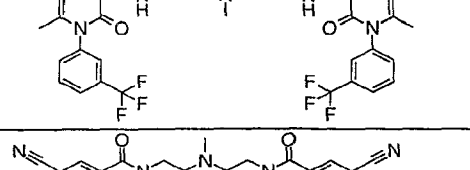
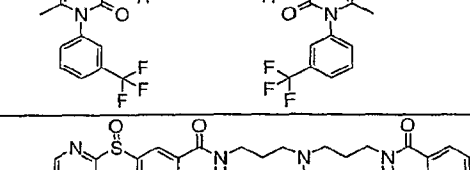
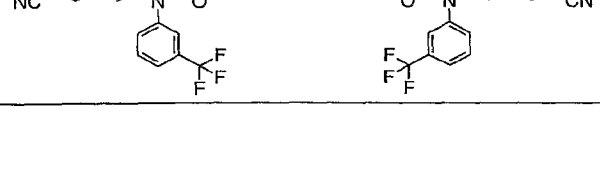
The results are means of two independent experiments, each performed in duplicate.

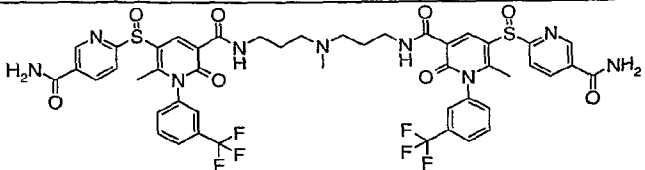
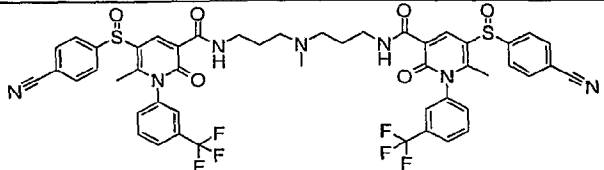
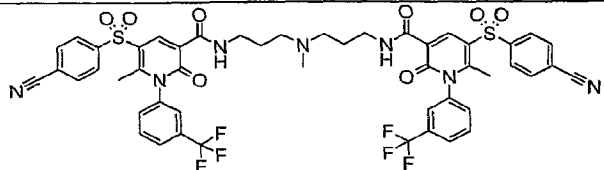
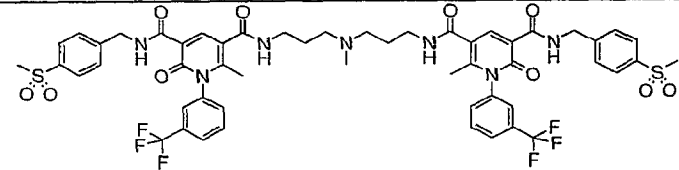
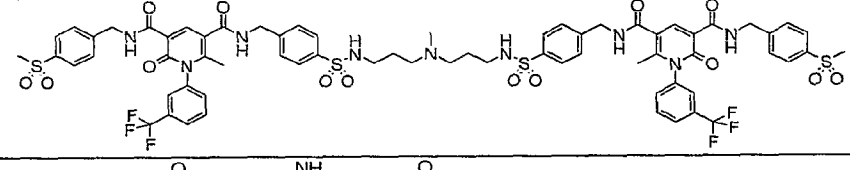
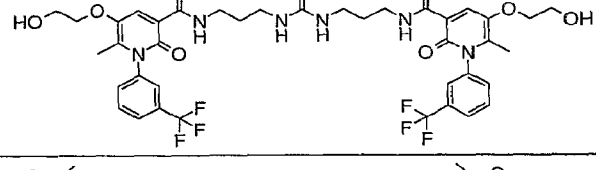
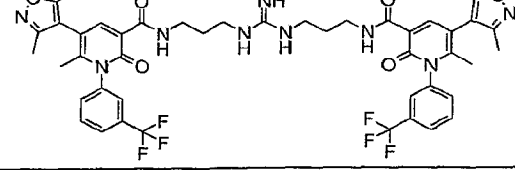
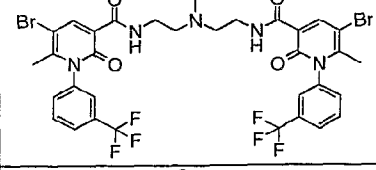
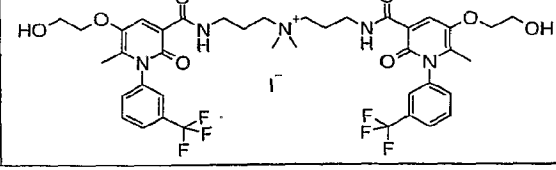
The compounds tested were shown to have IC_{50} values for HNE in the range 1-1000 nM. range A < 500 nM; B 500-1000 nM Range C >1000 nM. The results are reported

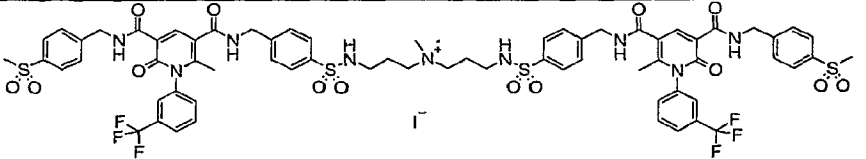
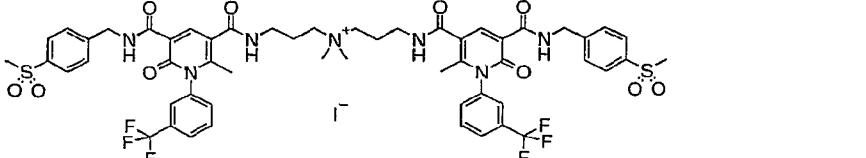
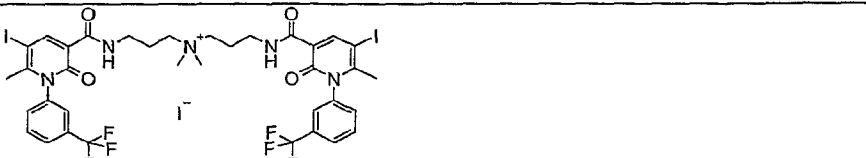
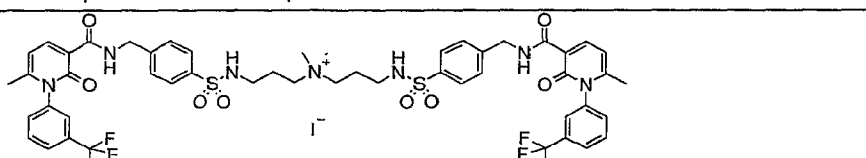
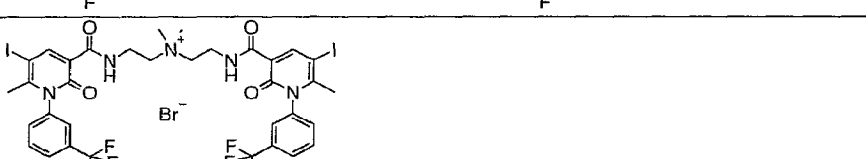
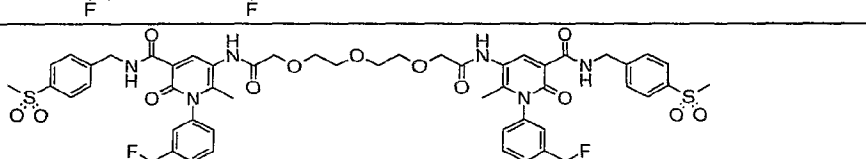
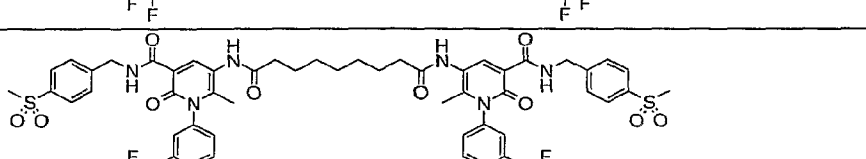
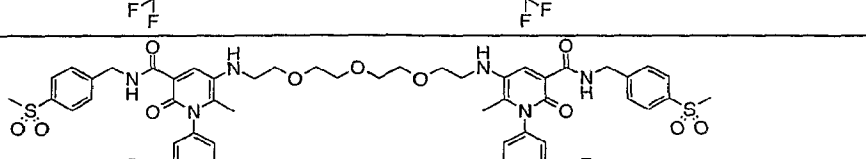
5 in the following Table:

TABLE

Example	Structure	Activity range*
1		A
2		A
3		A
4		B
5		B
6		A
7		C
8		A

9		A
10		C
11		A
12		C
13		A
14		A
15		C
16		C
17		A

18		B
19		A
20		A
21		A
22		A
23		C
24		A
25		C
26		C

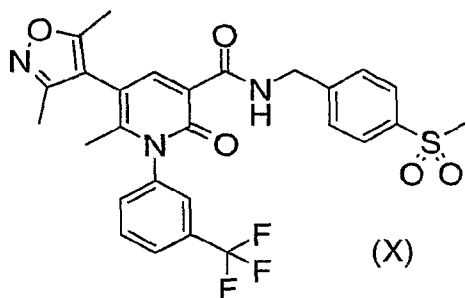
27		A
28		A
29		B
30		A
31		C
32		A
33		A
34		A

Key: A; IC₅₀ 1-500 nM
 B; IC₅₀ 501-1000 nM
 C; IC₅₀ >1000 nM

5

In the above Table, the actual IC₅₀ obtained for the compound of Example 3 was 49nM. The activity of the parent monomer (structure X below - disclosed in WO 2005/026123 (Example 11)) was found to be 6 nM in the same assay. Hence, the HNE inhibitory activity of the monomer is substantially retained in the dimer. The

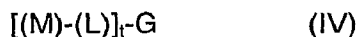
somewhat reduced intrinsic inhibitory activity of the dimer is tolerable since the dimer is primarily designed for pulmonary administration, where prolongation of activity relative to, for example, oral or even pulmonary administration of the monomer, is expected.



Claims:

1. A covalent conjugate of two or more compounds, each having a structure as defined in any of WO2004/043924, WO2005/021509, WO2005/021512, WO2005/026123, WO2005/026124, WO2006/098683 and WO2006/098684.

2. A covalent conjugate as claimed in claim 1 having the formula:

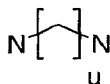
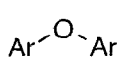


wherein

each M is independently a compound having a structure as defined in any of WO2004/043924, WO2005/021509, WO2005/021512, WO2005/026123, WO2005/026124, WO2006/098683 and WO2006/098684;

t is 2 to 20;

G is optionally substituted aryl or heteroaryl; C₁-C₆ alkyl; cycloalkyl; nitrogen; a dendrimer or a group of any of formulae (V) to (VII):



(V)

(VI)

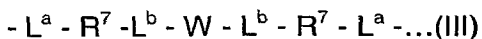
(VII)

wherein

Ar is aryl or heteroaryl; and

u is 2-20;

each L is independently a linker group of Formula (III)



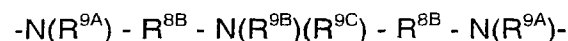
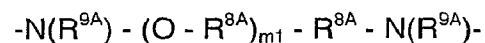
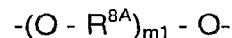
wherein

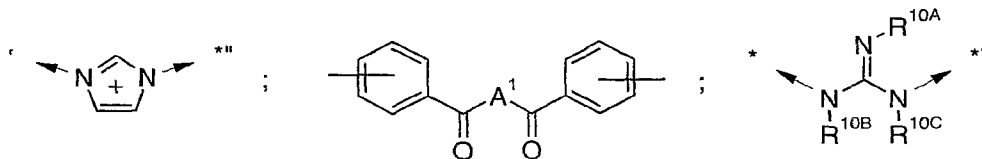
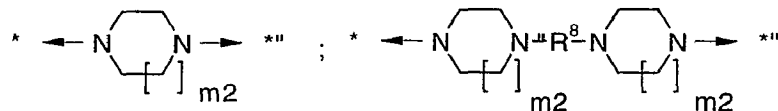
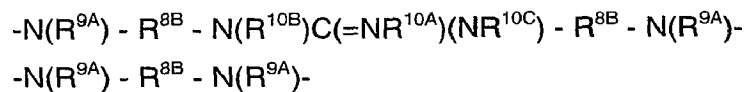
L^a is a bond or group -C(O)-;

L^b is a bond or group -C(O)-;

R⁷ is an alkylene or cycloalkylene group;

W is a bond or is selected from the following divalent radicals





wherein;

m1 is 1-4;

R^{8A} is an alkylene or cycloalkylene group;

R^{8b} is an alkylene or cycloalkylene group, or a group of Formula A²;

R^{9A} is hydrogen or alkyl;

one of R^{9B} or R^{9C} is a lone pair and the other is hydrogen or alkyl, or R^{9B} and R^{9C} are both alkyl, in which case the nitrogen to which they are attached is quaternary and carries a positive charge. Additionally, R^{9B} and R^{9C} may be joined together with the nitrogen to which they are attached to form a ring;

R^{10A} is hydrogen or alkyl;

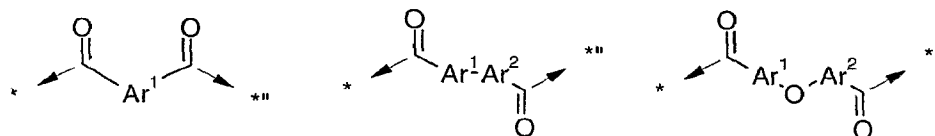
R^{10B} and R^{10C} are independently hydrogen or alkyl, or alternatively R^{10B} and R^{10C} may be joined together to form a ring;

m2 is 1-3;

A¹ is selected from the groups -N(R^{9A})-R⁸-N(R^{9B})(R^{9C})-R⁸-N(R^{9A})-, and

$$-N(R^{9A})-R^8-N(R^{10B})C(=NR^{10A})(NR^{10C})-R^8-N(R^{9A})-$$

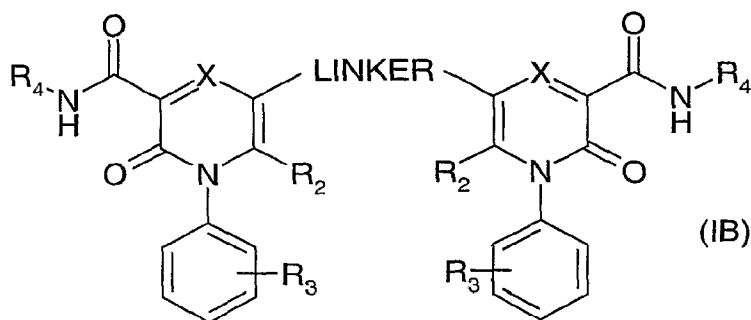
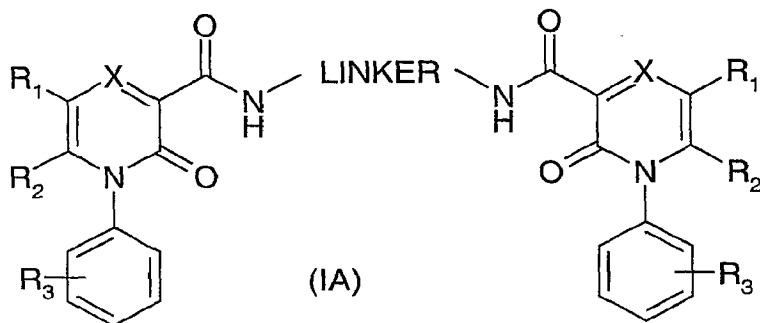
A^2 is selected from the groups of the formulae



wherein Ar¹, Ar² are independently an aryl or heteroaryl group;

or a pharmaceutically acceptable salt thereof.

3. A compound of formula (IA) or (IB), or a pharmaceutically acceptable salt thereof:



wherein

X represents -C= or -N=;

5

LINKER is a divalent linker radical;

R₁ is a group of formula Z-[Alk¹]_m-[X]_p-[Alk²]_n- wherein:

m, n and p are independently 0 or 1;

10

Z is hydrogen or an optionally substituted monocyclic carbocyclic or heterocyclic group having 3 to 7 ring atoms;

Alk¹ and Alk² are each independently an optionally substituted divalent C₁-C₆ alkylene, C₂-C₆ alkenylene or C₂-C₆ alkynylene radical, which may optionally be interrupted by -O-, -S-, -S(=O)-, -S(=O)₂- or -NR₅- wherein R₅ is hydrogen, C₁-C₃ alkyl, or cyclopropyl; and

15

X is -O-, -S-, -S(=O)-, -S(=O)₂- or -NR₅- wherein R₅ is hydrogen, C₁-C₃ alkyl, or cyclopropyl;

20

R₂ represents hydrogen or C₁-C₆ alkyl;

or in the case of formula (IA), R_1 and R_2 taken together with the carbon atoms to which they are attached form a 5-, 6- or 7-membered carbocyclic or heterocyclic ring fused to the ring containing X and N, said fused ring being optionally substituted by
5 one or more optional substituents, or one or more optionally substituted C_1 - C_3 alkyl, C_2 - C_3 alkenyl, or C_2 - C_3 alkynyl groups;

or in the case of formula (IB), R_2 is linked with a carbon or nitrogen atom in the LINKER radical to form a 5-, 6- or 7-membered carbocyclic or heterocyclic ring fused
10 to the ring containing X;

R_3 represents hydrogen, or 1 or 2 optional substituents, or 1 or 2 optionally substituted C_1 - C_3 alkyl, C_2 - C_3 alkenyl, or C_2 - C_3 alkynyl;

15 R_4 represents a radical of formula $-[Alk]_a-Q$ wherein

a is 0 or 1;

Alk represents an optionally substituted divalent C_1 - C_4 alkylene radical, which
20 may terminate in or be interrupted by $-O-$, $-S-$, $-S(=O)-$, $-S(=O)_2-$ or $-NR_5-$ wherein R_5 is hydrogen, C_1 - C_3 alkyl, or cyclopropyl;

Q is hydrogen, optionally substituted monocyclic carbocyclic or heterocyclic having from 3 to 6 ring atoms; or

25 R_4-NH- represents an optionally substituted monocyclic heterocyclic ring having 5 or 6 ring atoms and linked to the carbonyl via a ring nitrogen.

4. A compound as claimed in claim 3 wherein X is $-C=$.

30 5. A compound as claimed in claim 3 or claim 4 wherein R_2 is methyl.

6. A compound as claimed in any of claims 3 to 5 wherein R_3 represents 1 or 2 substituents, each independently selected from methyl, trifluoromethyl, fluoro, chloro,
35 bromo, C_1 - C_6 alkyl, $-CN$, C_1 - C_6 alkoxy, $-NO_2$, $-NR^A R^B$ wherein R^A and R^B are independently hydrogen or (C_1-C_6) alkyl, or R^A and R^B when attached to the same nitrogen form a cyclic amino group.

7. A compound as claimed in claim 6 wherein R_3 represents a trifluoromethyl substituent in the meta position of the phenyl ring relative to the point of attachment of that phenyl ring to the rest of the molecule.

8. A compound as claimed in any of claims 3 to 7 which has formula (IA), wherein R_1 is a group R_6 -Y- wherein R_6 is optionally substituted phenyl or monocyclic heteroaryl ring having 5 or 6 ring atoms, and Y is a bond, $-CH_2-$, $-C(=O)-$, $-O-$, $-S-$, $-S(=O)-$, $-S(=O)_2-$, or $-NH-$.

9. A compound as claimed in claim 8 wherein Y is $-S(=O)-$ and R_6 is optionally substituted phenyl or pyridyl.

10. A compound as claimed in claim 8 or claim 9 wherein R_6 is optionally substituted phenyl or pyridyl, in which optional substituents in the phenyl or pyridyl ring are selected from C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, methoxy, trifluoromethyl, trifluoromethoxy, cyano, fluoro, chloro, bromo, acetamino, sulfonic acid, $-NH_2$, $-NHR^A$, $-NR^A R^B$, $-NHCOR^A$, $-SO_2OH$, $-SO_2OR^A$, $-SO_2R^A$, $-SO_2NH_2$, $-SO_2NHR^A$, $-SO_2NR^A R^B$, $-OSO_2NH_2$, $-OSO_2NHR^A$, $-OSO_2NR^A R^B$, $-NHSO_2OR^A$, $-NR^B SO_2OH$, $-NR^B SO_2R^A$, $-NHSO_2R^A$ wherein R^A and R^B are independently hydrogen or $(C_1$ - $C_6)$ alkyl, or R^A and R^B when attached to the same nitrogen form a cyclic amino group.

11. A compound as claimed in claim 8 wherein R_6 is selected from oxazolyl, thiazolyl, imidazolyl, triazolyl, pyrazolyl, pyrazinyl, pyrimidinyl, oxadiazolyl, furyl, and thienyl, any of which being optionally substituted by C_1 - C_6 alkyl, C_1 - C_6 alkoxy, $-CN$, fluoro, chloro, bromo, or trifluoromethyl.

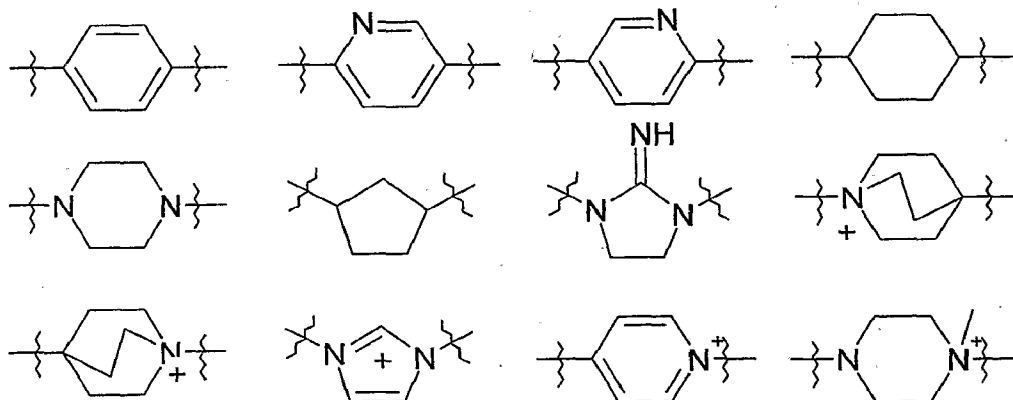
12. A compound as claimed in any of claims 3 to 7 which has formula (IB), wherein R_4 is benzyl, optionally substituted in the phenyl ring thereof.

13. A compound as claimed in any of claims 3 to 7 which has formula (IB), wherein R_4 is benzyl, optionally substituted in the 4-position of the phenyl ring thereof by a methylsulfonyl group.

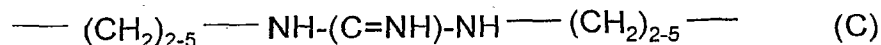
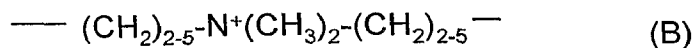
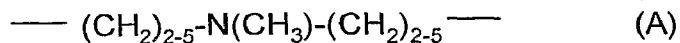
14. A compound as claimed in any of claims 3 to 13 wherein the LINKER radical is a divalent straight chain, saturated or unsaturated hydrocarbon radical having from

- 2 to 12 carbon atoms in the said chain, and wherein one or more carbons may be replaced by a divalent monocyclic or bicyclic carbocyclic or heterocyclic radical having from 3 to 7 ring atoms in the or each ring, or by -O-, -S-, -S(=O)-, -S(=O)₂-, -C(=O)-, -N(R^P)-, -N⁺(R^P)(R^Q)-, -C(=O)O-, -OC(=O)-, -C(=O)NR^A-, -NR^AC(=O)-, -S(O₂)NR^A-, -NR^AS(O₂)-, -NR^AC(=O)NR^B-, -NR^AC(=NR^A)NR^B-, -C(=NR^D)NR^E-, or -NR^EC(=NR^D)-, wherein R^A, R^B, R^D and R^E are independently hydrogen, C₁-C₆ alkyl, or C₃-C₆ cycloalkyl, and R^P and R^Q are independently hydrogen, C₁-C₆ alkyl, or C₃-C₆ cycloalkyl, HO-(C₁-C₆ alkyl)-, R^AR^BN-(C₁-C₆ alkyl)-, or HOC(=O)-(C₁-C₆ alkyl)-, or R^A and R^B, or R^D and R^E, or R^P and R^Q taken together with the nitrogens to which they are attached form a monocyclic heterocyclic ring of 5 to 7 ring atoms which may contain a further heteroatom selected from N, O and S.

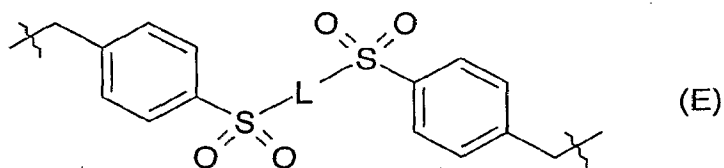
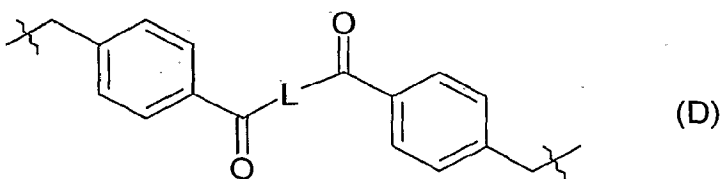
15. A compound as claimed in claim 14 wherein when one or more one or more -(CH₂)- groups of the LINKER radical is or are replaced by a divalent monocyclic or bicyclic carbocyclic or heterocyclic radical, the said radical is selected from the following:



16. A compound of formula (IA) as claimed in any of claims 3 to 12 wherein the LINKER radical has one of the following structures (A), (B) and (C):

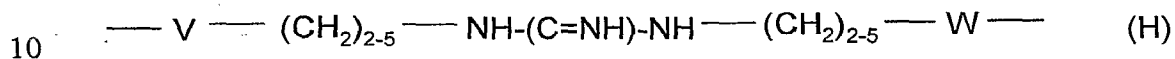
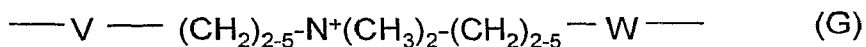
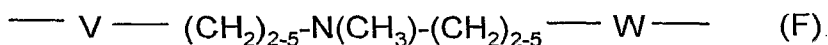


17. A compound of formula (IA) as claimed in any of claims 3 to 12 wherein the LINKER radical has one of the following structures (D) and (E):



5 wherein L is a radical of formula (A), (B) or (C) as in claim 15.

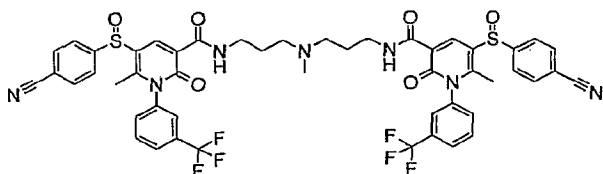
18. A compound of formula (IB) as claimed in any of claims 3 to 7 or 13 wherein the LINKER radical has formula (F), (G) or (H):

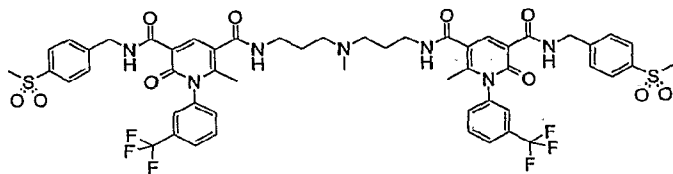
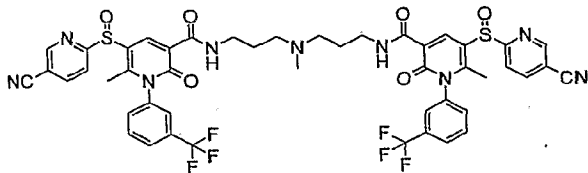
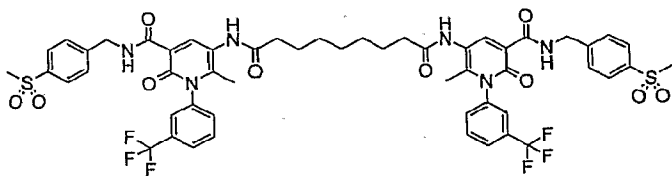


wherein -V- is selected from -O-, -C(=O)NH- in either orientation, -C≡C- and -NR^A-, and -W- is selected from -O-, -NHC(=O)- in either orientation, -C≡C- and -NR^A-, wherein R^A is (C₁-C₆)alkyl.

15 19. A compound as claimed in any of claims 3 to 18 wherein the LINKER radical contains a quaternary nitrogen.

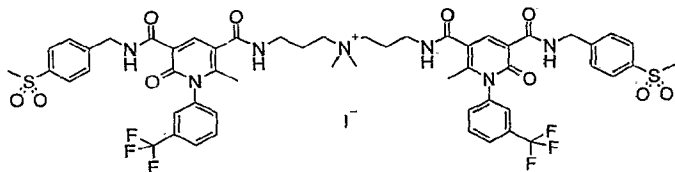
20. A compound as claimed in claim 3 having one of the following structures:





5.

and



21. A pharmaceutical composition comprising a compound as claimed in any of the preceding claims and a pharmaceutically acceptable carrier or excipient.

10

22. Use of a compound as claimed in any of claims 1 to 20, for the manufacture of a medicament for use in the treatment or prevention of a disease or condition in which HNE is implicated.

15

23. Use according to claim 22, wherein the disease or condition is chronic obstructive pulmonary disease (COPD), chronic bronchitis, lung fibrosis, pneumonia, acute respiratory distress syndrome (ARDS), pulmonary emphysema, smoking-induced emphysema or cystic fibrosis.

20

24. Use according to claim 22, wherein the disease or condition is asthma, rhinitis, psoriasis, dermatitis, (atopic and non-atopic), Crohn's disease, ulcerative colitis, and irritable bowel disease.